DISEASES of the CHEST

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The Diagnosis of Mediastinal Lymphoma by Thoracotomy*

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The differential diagnosis of isolated lymphadenopathy presenting as single or multiple tumors of the mediastinum found on x-ray examination of the chest may present considerable difficulty. The history, physical examination, skin sensitivity studies, bone marrow aspiration, peripheral blood examinations, and peripheral lymph node biopsies occasionally fail to establish a correct diagnosis. It has been an acceptable practice to treat such lesions empirically as lymphomas and to subject the patient to a trial of x-ray therapy.[1,2] With subsequent decrease in size of the tumor over a period of one to two months, it was assumed that the diagnosis of lymphoma was correct and no additional studies were performed to determine the accurate histologic diagnosis. Since nonspecific lymphadenopathy, tuberculosis, histoplasmosis, and Boeck's granulomas undergo spontaneous regression, or initially respond to radiation, such diagnostic radiation should be condemned. A series of cases considered to be lymphomas was studied at the Ohio State University Health Center in an attempt to point out the fallacy of trial radiation in patients with mediastinal lesions.

Materials and Results

In a 10-year period, from January 1950 to December 1959, there were 1652 admission to the University Hospital of patients with lymphomas. In the vast majority of these patients, the diagnosis of lymphoma presented no particular difficulty and specific therapy was instituted without delay. In 20 patients following the accepted diagnostic procedures the diagnosis of lymphoma remained uncertain, and rather than expose these patients to diagnostic x-ray therapy, a small anterior or posterolateral thoracotomy was utilized to obtain a representative lymph node for microscopic examination. Treatment was deferred until an accurate diagnosis based on the permanent microscopic section had been established.

The 20 patients fell into the younger age group in which lymphomas usually are prevalent. Ten patients were men, with an average age of 41 years and ten were women with an average age of 34 years. In only three was peripheral lymphadenopathy noted. Lymph node biopsies in

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TABLE 1—FINAL DIAGNOSIS OF 20 MEDIASTINAL TUMORS PRESUMED TO BE LYMPHOMAS

Tumor	No. of Cases
Benign: (total 13)	
Boeck's sarcoid	6
Granuloma	4
Teratoma	1
Lymphadenitis	1
Mesothelioma	1
Lymphoma: (total 7)	
Reticulum cell sarcoma	2
Hodgkin's disease	2
Lymphoblastoma	1
Lymphosarcoma	2
Total	20

these patients were not diagnostic nor were the peripheral blood count and bone marcrw studies. Skin sensitivity tests to tuberculin and histoplasmin antigens were negative in most instances.

Radiologic findings varied from generalized mediastinal and hilar lymphadenopathy to single densities projecting from the mediastinum. Peribronchial lymph node calcification was present in some patients but was found to be of no diagnostic value. None of the patients had peripheral pulmonary involvement.

Following the various appropriate diagnostic procedures a preoperative diagnosis of lymphoma was entertained in all these patients. With a limited thoracotomy and removal of a representative lymph node the preoperative diagnosis proved incorrect in 13 of the 20 cases while the diagnosis of lymphoma was correct in only sevent patients (Table 1).

Of the seven lymphomas, two were reticulum cell sarcomas, two were cases of Hodgkin's disease, two were lymphosarcomas, and one was a lymphoblastoma. The 13 benign lesions included four granulomas, six

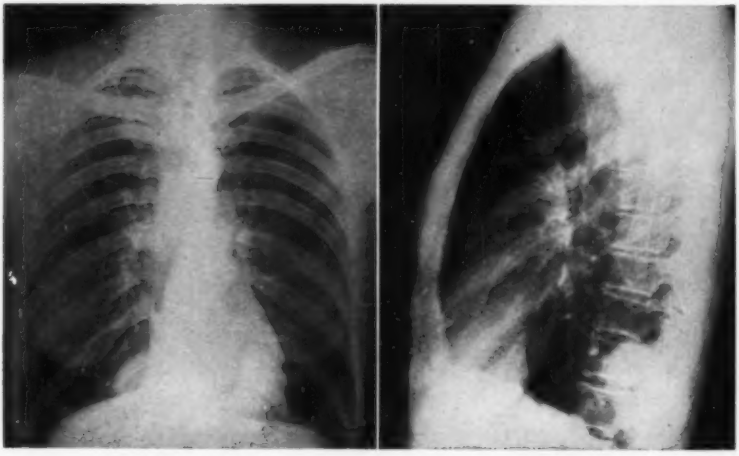

FIGURE 1A FIGURE 1B

FIGURE 1*a* and *b*: Roentgenogram of Case 1. Posterior mediastinal tumor following two courses of x-ray and nitrogen mustard therapy.

cases of Boeck's sarcoid, one teratoma, one mesothelioma, and one chronic nonspecific lymphadenitis.

There were 21 operations performed on these 20 patients. An anterior thoracotomy was utilized in 12 pa[illegible]nts and limited posterolateral thoracotomy in nine. One required a pos[illegible]olateral approach after an anterior thoracotomy failed to yield an adequate specimen for diagnosis.

Three brief case reports are presented to illustrate the value of a tissue diagnosis in patients with mediastinal lymphadenopathy.

Case 1. E.B. #539811A, a 49-year-old white woman was referred to the Ohio State University Health Center in November, 1953, with the complaint of pain in her left chest and easy fatigability. Roentgenograms of the chest in 1951 had shown a right inferior mediastinal mass interpreted as a lymphoma and treated with x-rays. Her symptoms had temporarily improved. The positive findings on admission to the hospital included generalized shotty lymphadenopathy and a liver edge 3 cm. below the right costal margin. The laboratory findings were a white blood count of 3,200 with 68 per cent neutrophils, 8 per cent lymphocytes, and 24 per cent monocytes. The hemoglobin was 12.7 gram per cent. Bone marrow aspiration showed an increased number of monoblasts and young monocytes, and this was interpreted hematologically as bone marrow invasion by reticulum cell sarcoma. Roentgenograms of the chest showed a right inferior mediastinal mass (Fig. 1a and b). Subsequently she was given a full course of nitrogen mustard as well as additional x-ray therapy.

She was relatively asymptomatic until November, 1956, when she was readmitted to the University Hospital with pain in both sides of her chest. X-ray film examination at this time showed an increase in the size of the mediastinal mass. Physical examination and laboratory data were unchanged from her previous admission. At exploratory thoracotomy the mediastinal mass was found to be a mesothelioma of the pleura. She was well and asymptomatic when last seen in June, 1959.

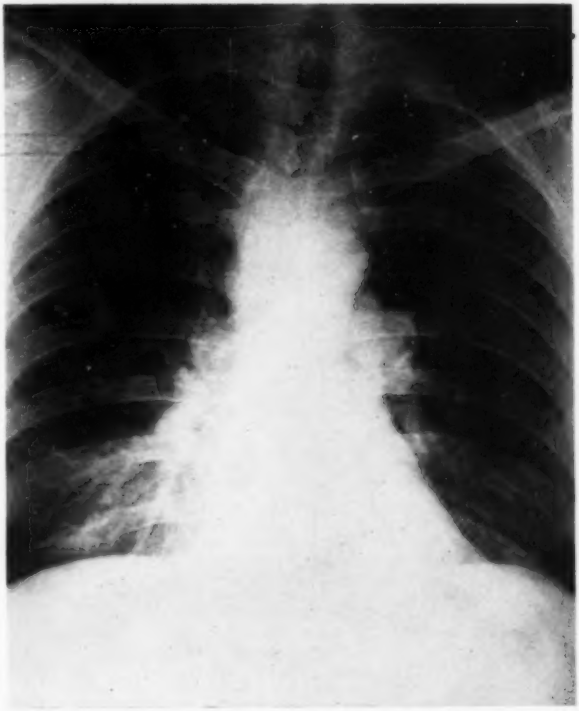

FIGURE 2: Roentgenogram of Case 2 showing right superior mediastinal mass with bilateral lymphadenopathy.

Case 2: H.S., #667256, a 44-year-old white man, entered the hospital on June 16, 1959 with the complaint of spots in front of his left eye. The only positive findings on examination were scotomata in the left visual field. Peripheral lymphadenopathy was absent and neurological examination including lumbar puncture and EEG was normal. The tuberculin and histoplasmin skin tests were negative. The peripheral blood count and bone marrow were normal. Routine x-ray films of the chest showed a mass in the right superior mediastinum, with increased hilar densities (Fig. 2).

He was believed to have a lymphoma and x-ray therapy was advised. A right anterior thoracotomy was performed and a large lymph node removed from the superior mediastinum. Examination of the specimen showed this to be a nonspecific mediastinal granuloma. He has remained asymptomatic and x-ray examination of the chest shows no abnormality.

Case 3: T.H., #641023, a 29-year-old white man, was admitted on May 4, 1958 with the complaint of a cold of two months duration characterized by fever, weakness, and a 25 pound weight loss. A routine mobile x-ray film examination was reported as showing spots in the perihilar region. Physical examination was within normal limits. Peripheral lymphadenopathy was absent. The peripheral blood and bone marrow examinations were noncontributory. A chest x-ray film showed bilateral symmetrical hilar lymphadenopathy (Fig. 4). Through an anterior thoracotomy a large lymph node was obtained. Permanent section showed this to be Boeck's sarcoid.

Discussion

Mediastinal lymphadenopathy, presenting minimal symptoms of short duration or found on x-ray film survey of population groups,[3,4] requires accurate histologic diagnosis prior to the institution of any form of therapy. The history of the presenting complaints or other factors in the patient's background may be of help in suggesting a definite diagnosis. Association with open tuberculosis cases in young individuals may lead to tuberculous lymphadenopathy, while residence in heavily infected areas of histoplasmosis may give rise to similar mediastinal lymph node enlargement. Calcification is absent in early stages of these granulomas.

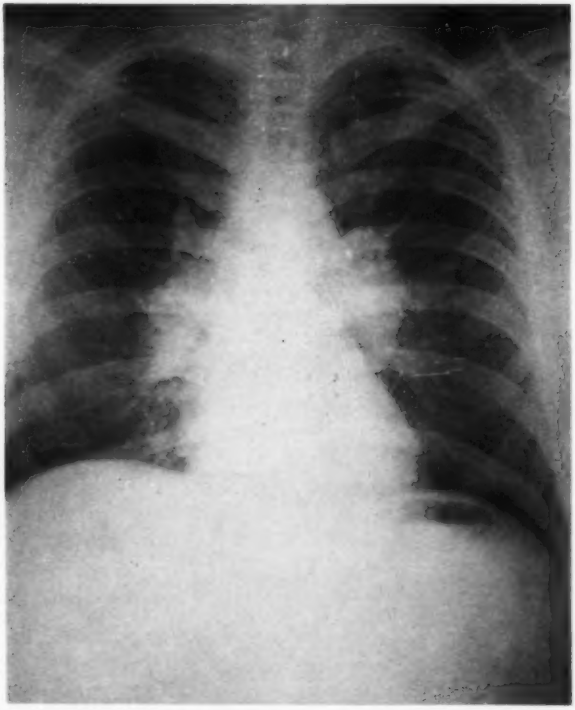

FIGURE 3: Roentgenogram of Case 3 showing bilateral hilar adenopathy which proved to be Boeck's sarcoid after biopsy.

Physical examination in the majority of patients with lymphomas will reveal the presence of peripheral lymph node enlargement and biopsy of these nodes usually leads to a correct diagnosis. In a fairly large number of patients with mediastinal lymphadenopathy, cervical lymph node biopsy is not diagnostic,[5] for in lymphomas as well as in benign lesions such as Boeck's sarcoid, tuberculosis, and histoplasmosis, enlarged peripheral lymph nodes on biopsy may show nonspecific hyperplasia and lead to an erroneous diagnosis. Elevation of the venous pressure in the upper extremity is usually assumed to be secondary to complete occlusion of the superior vena cava by an invading mediastinal neoplasm. The superior vena caval syndrome is frequently encountered in patients with advanced lymphosarcoma and Hodgkin's disease of the mediastinum. Complete obstruction of the superior vena cava may occur in young individuals with chronic mediastinitis secondary to involvement of the mediastinal lymph nodes by histoplasmosis and tuberculosis,[6] as well as on rare occasions by intrathoracic goiters. The presence of a superior vena cava syndrome does not always indicate the presence of malignancy in the mediastinum. The most frequent cause of such occlusion in the older age group is secondary to mediastinal involvement by a bronchogenic carcinoma.[5]

Skin sensitivity tests for histoplasmosis and tuberculosis have been of some help in the differential diagnosis of mediastinal lymphadenopathy. It is generally agreed that negative skin tests to histoplasmosis and tuberculosis in a patient with diffuse involvement of the lung or mediastinal lymphadenopathy is strong suggestive evidence for the presence of Boeck's sarcoid. However, with decreased incidence of tuberculosis and the absence of evidence of histoplasmosis in large areas of this country, negative tuberculin and histoplasmin skin reactions under these conditions do not necessarily indicate the diagnosis of Boeck's sarcoid in the presence of mediastinal lymphadenopathy.

Laboratory examination of the peripheral blood and bone marrow by standard and supravital stain techniques will in most cases of advanced lymphosarcoma and Hodgkin's disease reveal changes diagnostic of these conditions. However, in early cases of lymphosarcoma, frequently limited to the mediastinum, such peripheral blood and bone marrow studies are frequently negative. In Boeck's sarcoid the peripheral blood picture is normal, however, bone marrow studies may show the presence of atypical monocytes.[7] These cells have on occasion been confused with abnormal cells of lymphomas.

Special x-ray studies in addition to the routine anteroposterior chest projection may occasionally be of help in differentiating the various malignancies of the mediastinum.[4] Lymphadenopathy of malignant and benign origin as such cannot be differentiated by this method, and very little is added by such studies as laminography, bronchography, an dfluoroscopy except to pinpoint definitely the intrathoracic density to hilar and mediastinal lymph nodes as against bronchial, esophageal, or pulmonary locations. Contrast studies of the esophagus and bronchus are quite helpful in that intraluminal obstruction by neoplasms can be differentiated from the deformity produced by enlarged perilluminal lymph nodes. The presence or absence of calcification in itself is of little value since malignant lymphosarcomas may occur in or adjacent to tuberculous and histoplasmotic lymph nodes. Bacterial studies in the absence of pulmonary lesions are nonproductive in patients with mediastinal lymphadenopathy. Supraclavicular lymph node biopsy, although quite rewarding in patients with Boeck's sarcoid and bronchogenic carcinoma, will frequently be negative. An accurate diagnosis of mediastinal malignancy occasionally requires thoracotomy and removal of a representative lymph node from the peribronchial or mediastinal area.

Review of our series of 20 patients indicates that a diagnosis of malignant mediastinal lymphoma must be based on the microscopic section of a representative intrathoracic lymph node prior to institution of any type of therapy. A thoracotomy and direct biopsy makes a diagnosis simple and accurate without delay in time and should be a part of the diagnostic armamentarium of everyone dealing with this particular problem. A standard large thoracotomy incision is not necessary since the exposure is made only for the removal of a specific lymph node, these nodes being removed without difficulty in most instances. A large posterior thoracotomy is associated in itself with a blood loss of some 500 cc. and for this reason we have used a limited small posterolateral or posterior thoracotomy without removal of ribs.

In the anterior thoracotomy approach, a small "hockey stick" shaped incision is made parallel with the clavicular and sternal margin, the pectoralis major muscle is split, and the second or third intercostal space exposed. The intercostal muscles are cut and one or two costochondral junctions are divided if necessary for adequate exposure. The mediastinum is entered and either an entire or piece of lymph node is obtained. The advantages of this approach include supine position requiring no intubation, operating time averaging 30 minutes, little blood loss, reduced postoperative pain and discomfort, and brief convalescence. The disadvantages of this incision are poor cosmetic results in women, poor exposure in the event of technical difficulties, and inability to expose adequately the posterior mediastinum. The posterolateral incision can be confined to an 8 to 10 centimeter length, can easily be extended in case resection of the tumor is possible, and offers better exposure of the mediastinum. The disadvantages of the posterolateral incision are greater postoperative pain, longer operating time, lateral position on the operating table, and necessity for intubating the patient.

There was no operative death in our 20 patients. A correct diagnosis was established in all cases, and proper therapy was begun before these patients were discharged from the hospital.

SUMMARY

Twenty patients with a presumptive diagnosis of malignant lymphoma of the mediastinum were observed in a 10 year period. In the absence of cytologic proof of malignant lymphoma, a limited thoracotomy for the removal of a representative mediastinal lymph node was performed.

In only seven patients was the diagnosis of malignant lymphoma proved to be correct, while 13 were found to have benign lesions.

RESUMEN

Se observaron viente enefrmos con el diagnóstico de presunción de linfoma maligno del mediastino durante 10 años. A falta de prueba citológica del linfoma maligno, se hizo una toracotomía para quitar un ganglio mediastínico representativo de la enfermedda.

S'lo en siete enfermos el diagnóstico de linfoma maligno fué correcto, en tanto que en los 13 restantes se trataba de formaciones benignas.

RESUMÉ

20 malades atteints, selon le diagnostic présumé, de lymphome malin du médiastin, furent observés pendant une période de 10 ans. En l'absence de preuve cytologique de lymphome malin, une thoracotomie limitée pour l'exérèse d'un ganglion médiastinal caractéristique fut pratiquée.

Chez 7 malades seulement, le diagnostic de lymphome malin fut mit en évidence, tandis que 13 furent trouvés porteurs de lésions bénignes.

ZUSAMMENFASSUNG

Im Verlauf einer Zeitspanne von 10 Jahren gelangten 20 Kranke mit der Vermutungsdiagnose eines bösartigen Lymphoms des Mediastinums zur Beobachtung. Bei Fehlen einer cytologischen Bestätigung eines bösartigen Lymphoms wurde eine begrenzte Thorakotomie zum Zweck der Gewinnung eines geeigneten mediastinalen Lymphknotens vorgenommen.

Nur bei sieben Patienten erwies sich die Diagnose eines malignen Lymphoms als korrekt, wohingegen sich bei 13 Patienten gutartige Veränderungen fanden.

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Lung Cancer in Women*

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The prevalence of lung cancer has increased markedly over the past thirty years;[1,2] most of the rise has been among men but there has been some increase among women (Fig. 1). It would be desirable to inaugurate a study of women comparable to the Philadelphia Pulmonary Research Project[3] for men but, if the prevalence of 1/100,000 reported by Boucot and Sokoloff[4] in 1955 is correct, the yield would be so small that an enormous basic population would be required.

This paper is concerned with 102 cases of proved lung cancer in women diagnosed in Philadelphia hospitals between 1948 and 1950.

Method

In 1955, permission was sought from 43 Philadelphia hospitals[5] to search their records from January 1948 through December 1950 for proved cases of lung cancer among women. Cases were followed through December, 1955, yielding a minimal interval of five years from the date of diagnosis.

Of the 43 hospitals, two had no indices for the years specified, a third would not open its records without the consent of both patient and physician, an obvious impossibility, and a fourth hospital did not cooperate. Thus, the records of 39 hospitals were actually examined.

A questionnaire containing 18 items was designed. Data from hospital

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TABLE 1 — MORTALITY BY YEARS AFTER TISSUE DIAGNOSIS AMONG 102 PROVED CASES OF BRONCOGENIC CARCINOMA IN WOMEN

Time following diagnosis in years	TOTAL			NOT EXPLORED[1]			EXPLORED NOT RESECTED			EXPLORED RESECTED[2]		
	Number at risk	Deaths No.	Deaths Per cent	Number at risk	Deaths No.	Deaths Per cent	Number at risk	Deaths No.	Deaths Per cent	Number at risk	Deaths No.	Deaths Per cent
0 to 1	102	79	77.	53	46	87.	21	17	81.	28	16	58.
1 to 2	23	15	65.	7	7	*	4	3	*	12	5	18.
2 to 3	8	4	*	—	—	—	1	—	—	7	4	*
3 to 4	4	1	*	—	—	—	1	1	*	3	—	—
4 to 5	3	—	—	—	—	—	—	—	—	3	—	—
5 to 6	3	—	—	—	—	—	—	—	—	3	—	—
TOTAL	—	99	97.	—	53	100.	—	21	100.	—	25	90.

[1] Includes three women who refused surgery
[2] Includes one woman explored against medical advice
* Base too small for statistical significance

TABLE 2 — DISTRIBUTION ACCORDING TO AGE AND RACE OF 102 PROVED CASES OF BRONCHOGENIC CARCINOMA IN WOMEN

AGES	BOTH RACES		WHITE	NON-WHITE
	Number	Per cent	Number	Number
All ages	102	100.	95	7
Under 25	1	1.	1	0
25 — 44	13	13.	11	2
45 — 64	57	56.	53	4
Over 65	31	30.	30	1

records were abstracted and entered on these questionnaires except in two instances where use was made of previously prepared abstracts developed by teaching hospitals engaged in lung cancer research.

Age, race, tissue type, bronchoscopic findings and delay between onset of symptoms and hospitalization resulting in diagnosis were studied. Survival rates were calculated from the date of tissue diagnosis. Operative mortality was based on all deaths within one month of surgery as well as deaths from complications obviously attributable to the surgery. Delay was defined as any interval longer than three months between the onset of symptoms and hospitalization. Cases were accepted as proved in which uniquivocal tissue diagnoses were available, or, in 15 instances, where cytologic diagnosis was supported by clinical course.

Where there was more than one primary cancer, the histologic sections were reviewed and only those cases were accepted as primary lung cancer in which the reviewer excluded the possibility that the lung tumor was metastatic. Non-malignant associated conditions were noted.

Follow-up information was sought from tumor clinics, referring physicians, nearest of kin, death certificates and other sources such as the telephone company, recorders of deeds, church records, the Social Security Administration and the Post Office.

Results

One-hundred thirty-eight clinically diagnosed cases of bronchogenic carcinoma were found at 18 hospitals. One-hundred two of these cases met the criteria for proof of primary lung cancer.

Surgical Considerations

Exploration had been recommended for half of the 102 cases. Three women refused thoracotomy and one woman insisted upon exploration

TABLE 3 — TISSUE DIAGNOSES IN PROVED LUNG CANCERS BY SEX*

TISSUE DIAGNOSES	WOMEN IN THIS SERIES		MEN IN OFFICIAL PHILADELPHIA SURVEYS[11]	
	Number of Cases	Per cent	Number of Cases	Per cent
ALL TYPES	102*	100.	228*	100.
Squamous cell	26	26.	123	54.
Adenocarcinoma	31	30.	33	15.
Undifferentiated	32	31.	63	28.
Terminal bronchiolar cell	4	4.	2	1.
Not specified	9	9.	7	3.

* 102 women reported in this paper, and 228 men among 250 consecutive proved lung cancer cases in Official Philadelphia Surveys.

against medical advice. Forty-nine cases, (48 per cent) were explored. Operative mortality for those explored was 6 per cent. This rate is lower than Gibbon et al's[6] 13 per cent for 246 patients and Ochsner's[7] 18 per cent for 777 patients.

Twenty-eight women were resected, a resection rate of 27 per cent, about that for both sexes reported in many surgical series.[8,9,10] Resection rates for females alone are not available in the literature. In a series of 250 consecutive survey-detected lung cancer cases[11] there were 228 men. Sixty-seven (29 per cent) of the men were resected.[12] Of the small group of 22 women, six were resected.[12]

Survival

The length of survival of those who die is a reflection of the stage of the disease at the time of tissue diagnosis as well as of the rate of tumor growth. Seventy-seven per cent of the women died within one year of the date of tissue diagnosis (Table 1).

There were only three five-year survivors, an over-all five year survival rate of 3 per cent, somewhat worse than the over-all survival figures reported in the literature. The three five-year survivors had been resected.

Of the 26 women with squamous cell tumors, five lived one year and none lived two years. Of the 31 with adenocarcinomas, eight lived one year, two lived two years, and only one five years after diagnosis. Those with undifferentiated carcinoma had the best prognosis—nine of the 32

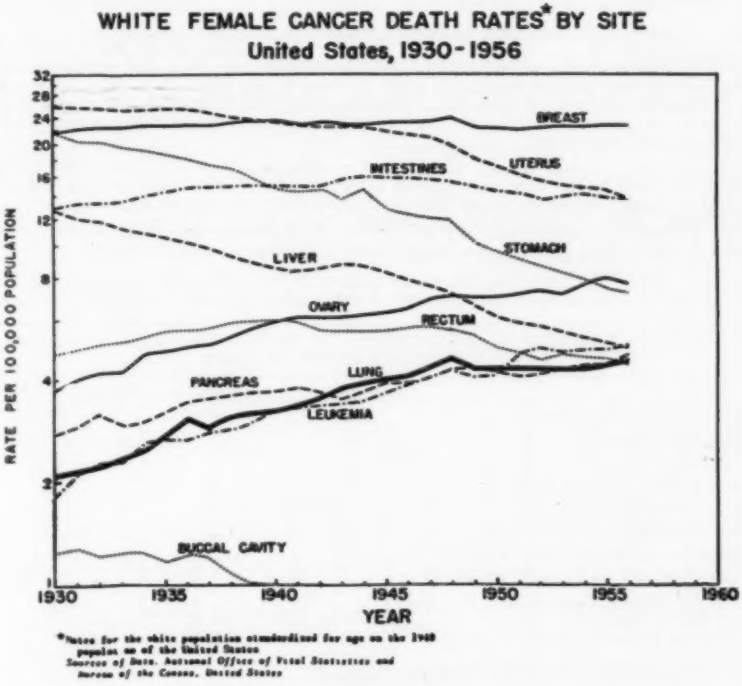

FIGURE 1

TABLE 4 — SITE OF TISSUE SPECIMENS AMONG 102 PROVED CASES OF BRONCHOGENIC CARCINOMA IN WOMEN*

SOURCE OF TISSUE		NUMBER
Lung		55
Resected specimen	28	
Biopsy	27	
Bronchus		53
Biopsy	21	
Secretions	32	
Extrapulmonary tissue		28
Lymph node biopsy	11	
Pleural fluid	16	
Bone marrow	1	
Autopsy specimen		21
Diagnosis made only at post	10	

* Categories not mutually exclusive

lived one year, five two years, two three years, and one five years. Of the four terminal bronchiolar carcinomas, three died within one year of diagnosis. The fourth lived five years.

Case histories of the three five-year survivors are as follows:

Case 1: *Mrs. M.C.*, a 61-year old white housewife, had a survey photofluorogram on August 1, 1949, which was read as "suspect neoplasm." She was asymptomatic but that week was admitted to Jefferson Hospital. Bronchoscopic findings, both gross and microscopic, were negative. On August 15, 1949, a right lower lobe resection revealed undifferentiated cancer. This woman was last seen on July 31, 1956, almost seven years after resection.

Case 2: *Mrs. L.S.*, a 65-year old white housewife, was first seen in August of 1948 complaining that for six months she had had persistent cough associated with hemoptysis and unexplained anorexia with ensuing weight loss. She was hospitalized at Pennsylvania Hospital on August 8, 1949. A chest x-ray film taken August 20, 1949, was interpreted as "suspect neoplasm." Bronchoscopic findings, both gross and microscopic, were normal. A right lower lobe resection on August 29, 1949, revealed terminal bronchiolar cell carcinoma.

She remained entirely asymptomatic but a routine follow-up x-ray film in 1956 revealed changes in the basilar segments of the left lower lobe. Four basilar segments resected in April of 1956 revealed terminal bronchiolar cell carcinoma.

She was alive and apparently well on July 15, 1958, almost seven years after her first lobectomy and about two and one-half months after the second resection.

Case 3: *Mrs. S.T.*, a 63-year old white housewife, was first seen on March 15, 1950, complaining of severe cough for over two years, hemoptysis for one month and unex-

TABLE 5 — RESECTION ACCORDING TO BRONCHOSCOPIC FINDINGS AMONG SEVENTY-SEVEN WOMEN

	Number	Resected	Per cent Resected
*Normal Gross Appearance**	*33*	*18*	*55.*
Negative cytology	23	15	65.
Positive cytology	10	3	30.
Abnormal Gross Appearance	*44*	*8*	*18.*
No cytology, no biopsy	3	**	**
No cytology, positive biopsy	11	2	18.
Negative cytology, no biopsy	9	3	**
Negative cytology, positive biopsy	2	**	**
Positive cytology, no biopsy or negative biopsy	10	2	20.
Positive cytology, positive biopsy	9	1	**

* Obviously biopsies could not be taken

** Base too small for statistical significance

plained weight loss. A chest x-ray film taken by a private physician was read as "suspect neoplasm." She received 10 x-ray treatments administered by a private radiologist.

On April 21, 1950, she was admitted to Temple University Hospital. "Palliative" left lower lobe lobectomy on April 28, 1950, revealed adenocarcinoma. She remained well until a myocardial infarction in January of 1952, from which she recovered satisfactorily. In November, 1955, she complained of cough of two weeks' duration but a chest x-ray film revealed no evidence of recurrence. Early in 1956 she suffered a cerebrovascular accident with hemiparesis of the left side. In addition, arthritic symptoms manifested themselves in a few of the larger joints. At various times she appeared abnormally depressed.

Despite these handicaps, she was up and about and performed some of her household chores. She was alive on July 13, 1956, more than six years after resection and about one year after the cerebrovascular accident.

Age and Race

Table 2 presents the cases by age and race. Eighty-six per cent of the women were older than 45, the usual situation in lung cancer series. There were no statistically significant differences in resectability between younger and older women. The three five-year survivors were 61, 63, and 65 years of age respectively, suggesting the possibility that older women with lung cancer may have a more favorable prognosis.

Ninety-five of the women were white and seven were non-white.

Tissue Type

The proportion of squamous cell carcinoma, adenocarcinoma, and undifferentiated carcinoma was roughly the same—about one-third in each category (Table 3). The proportion differs from that among 228 men with lung cancer at two official Philadelphia survey units[11] (Table 3). Tissue diagnoses for the 22 women in the Philadelphia survey study[11] were squamous cell, four cases, adenocarcinoma 10, undifferentiated seven, and unclassified one.

Wynder et al,[12] reporting in 1956 on a series of 196 histologically proved lung cancers among women, found a preponderance of adenocarcinoma. Their figures were epidermoid—32 per cent (62 cases), adenocarcinoma

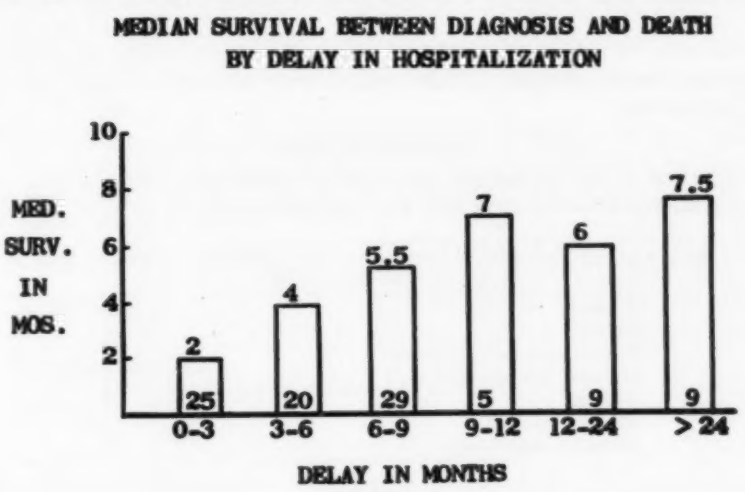

FIGURE 2

42 per cent (82 cases), anaplastic 18 per cent (35 cases), unclassified 8 per cent (16 cases).

All surgical series, predominantly men, report a preponderance of squamous cell carcinoma, from 53 per cent reported by Ochsner et al[7] in 1956, to 60 per cent by Overholt and Bougas[14] in the same year.

The sites from which tissue diagnoses were made are listed in Table 4. It was noteworthy that 10 per cent of the series were diagnosed only at autopsy. One of these had miliary nodulations and another superior vena caval obstruction. This 10 per cent figure is about the same as that for the 228 men in official Philadelphia surveys.[13]

The three five-year survivors had three different types of cancer—undifferentiated, adenocarcinoma, and terminal bronchiolar carcinoma. *The only microscopic evidence of tumor obtained in their cases was from the resected specimens;* bronchoscopy revealed no gross abnormalities and cytologic studies of bronchial secretions were also negative.

Bronchoscopic Findings

Of the 77 patients bronchoscoped, 33 appeared normal on inspection, while 23 had normal cytologic findings as well. Of these 23, 15 were resected (Table 5). The five-year survivors are among this group with both gross and cytologic normal findings. Table 6 lists the gross bronchoscopic findings.

In three instances, positive cytology was the only preoperative proof of cancer. One of these, with anaplastic carcinoma, was explored but not resected because of extensive metastases. She lived four months after the tissue diagnosis and only eight months after the pneumonitis with which her first symptoms were associated. The other two, both with adenocarcinomas, were resected but lived only four and 13 months respectively.

Twenty-five patients were never bronchoscoped. Of these, four were not suspected of having lung cancer but were diagnosed at autopsy, 12 had proved metastases—three by lymph node biopsy, one by bone marrow biopsy, and eight by the detection of tumor cells in pleural fluid. Three had central nervous system involvement thought to be due to metastases. Six were explored at five different institutions without having been bronchoscoped. Three women were actually resected without bronchoscopy.

Symptomatology

Only one of the 102 women was known to have been asymptomatic. She was a survey-detected case who was resected, found to have an undiffer-

TABLE 6 — GROSS BRONCHOSCOPIC FINDINGS ON SEVENTY-SEVEN LUNG CANCER CASES*

Normal	33
Tumor	19
Compression or distortion	14
Mucosal thickening**	7
Stenosis	4
Bloody secretion	2
Excessive secretion	2

* Categories not mutually exclusive
** Positive biopsy in four instances

TABLE 7 — SYMPTOMS AMONG 97 WOMEN WITH PROVED LUNG CANCER

Symptom*	Number	Per Cent of 97
Cough	75	77.
Unexplained weight loss	50	52.
Pain or tightness in chest	42	43.
Dyspnea	33	34.
Hemoptysis	30	31.
Fatigue	21	22.

* Categories not mutually exclusive

entiated carcinoma, and was living at the time of the last check-up more than five years after diagnosis. A second was disoriented so that no history was obtainable. Three had symptoms attributable only to cerebral metastases. Table 7 lists respiratory and general symptoms according to frequency for the other 97 women.

In Gibbon et al's[15] series of 532 cases, largely men, symptoms occurred in the same order of frequency as in the above list but each symptom was of a higher magnitude than in this series of women.

The 32 per cent hemoptysis rate for the 97 older men with cancer in the Philadelphia Pulmonary Neoplasm Research Project[16] was identical with the figure for the 97 women. Since hemoptysis is a dramatic symptom, memory in regard to it is apt to be reliable. Among the Philadelphia Pulmonary Neoplasm Research Project men, cough occurred in 80 per cent—about the same figure as among the women. Pain or heaviness in the chest occurred in 66 per cent of the men, compared to 43 per cent of the women, while weight loss occurred in 33 per cent of the men and in 52 per cent of the women.

Twenty-three women gave a history of antecedent acute respiratory infections in which persistent cough and weight loss of more than 10 pounds followed the episode. Medical treatment had been prescribed for "grippe," "bronchitis," "virus pneumonia," "virus X," "pneumonia with pleurisy," "pneumonitis," "bronchial asthma," "bronchopneumonia," and "double pneumonia." The length of treatment for these conditions varied from two weeks to one year with a median of five months before hospitalization.

Nine women sought treatment only because of extrapulmonary symptoms—a rate of 9 per cent, about the same as that reported by Leader and Borgelson[17] in their series of 2000 cases of primary lung cancer, all but one of whom were men.

TABLE 8—DELAY BETWEEN SYMPTOMS AND HOSPITALIZATION IN 97 SYMPTOMATIC WOMEN WITH LUNG CANCER

Delay in Hospitalization (months)	Number of Cases	Per Cent of 97
OVER-ALL TOTAL	97	100.
No delay— 0 to 3	25	26.
3 to 6	20	20.
6 to 9	29	30.
9 to 12	5	6.
12 to 24	9	9.
over 24	9	9.

Metastases at the Time of Diagnosis

Twenty-eight of the 102 women had metastases at the time of diagnosis (Table 4). This does not adequately reflect the advanced state of their malignancies at the time of histologic proof. The existence of pleural effusion in 16 per cent is amazingly high. Three had involvement of nerves—in one instance, the recurrent laryngeal, in another the phrenic and, in the third, both recurrent laryngeal and phrenic.

There were four whose presenting problems were associated with metastases, as follows:

Case 4: Mrs. K. B., a 45-year old white housewife noted a firm, round, painless mass in each supraclavicular area in January of 1948. In March the mass on the right began to grow. She was admitted to Philadelphia General Hospital on May 25, 1948. A chest film on May 27, 1948, was interpreted as "Irregular, uniform dense area occupying lower posterior portion of right upper lobe; malignancy must be considered."

Lymph node biopsy on June 1, 1948, revealed adenocarcinoma, metastatic from the lung. Bronchoscopic examination was not done. She was dicharged on June 2, 1948. She died in Philadelphia General Hospital on December 5, 1948, 11 months after the appearance of the supraclavicular masses. Permission for autopsy was not obtained.

Case 5: Mrs. H.G., a 58-year old white housewife, noted dimming vision in her right eye in August of 1949. Retinal detachment occurred shortly thereafter. She was admitted to Graduate Hospital November 9, 1949, for enucleation of the right eye. This revealed metastatic adenocarcinoma. A chest film taken November 15, 1949, revealed a moderate-sized, fairly well circumscribed, rounded opacity in the right upper lung field. This lesion was interpreted as "either neoplasm with central necrosis or tuberculosis with cavitation."

Both gross and microscopic findings at bronchoscopic examination on November 22, 1949, proved negative. Thoracotomy on December 4, 1949, revealed inoperable adenocarcinoma.

She died on July 21, 1950, about a year from the time she had first sought medical aid for her eye symptoms.

Case 6: Mrs. E.H., a 66-year old white housewife, noted lumbar backache, pain in her legs, anorexia and weight loss following a fall in April of 1950. She was admitted to St. Mary's Hospital on July 9, 1950. Clinical impression on admission was malignancy of the kidney.

A chest film taken on the following day described a lesion in the left lung which appeared metastatic rather than primary. However, a clinical diagnosis of primary bronchogenic carcinoma was made before she was discharged on August 13, 1950. On August 29, 1950, she was admitted to Pennsylvania Hospital in poor condition, lingering there until her death on November 12, 1950, about seven months after the onset of symptoms.

At autopsy the lesion in the left lung proved to be a primary undifferentiated bronchogenic carcinoma. There were widespread metastases but none to the kidneys.

Case 7: Mrs. I.T., a 62-year old white housewife, was admitted to Graduate Hospital on July 24, 1950, complaining of low back pain radiating to the right hip. She related the onset of pain to a minor back injury.

The chest film of July 25, 1950, was read as "Changes due to a primary bronchogenic malignancy with secondary partial atelectasis of the right upper lobe." Bone marrow obtained from the left iliac crest on July 29, 1950, revealed oat cell carcinoma. She was discharged on August 14, 1950.

She died at home on January 6, 1951, a little over six months following the onset of symptoms.

TABLE 9—DELAY IN HOSPITALIZATION ACCORDING TO TISSUE TYPE IN 97 SYMPTOMATIC WOMEN WITH LUNG CANCER

	Length of Delay				
	Unknown	More than 6 Months	6 Months to 1 Year	More than 1 Year	Total
TOTAL	1	44	34	18	97
Squamous	—	11	10	4	25
Anaplastic	1	13	10	4	28
Adenocarcinoma	—	17	7	7	31
Terminal Bronchiolar	—	1	2	1	4
Unspecified	—	2	5	2	9

Delay in Diagnosis

Table 8 lists delay between onset of symptoms and hospitalization. All of the 25 women hospitalized without delay died. Two women lived five years despite a delay of six months in a case of terminal bronchiolar carcinoma (Case 2), and more than two years in a case of adenocarcinoma (Case 3). In the latter case, persistent cough and weight loss had been present for over two years but hemoptysis occurred only one month before hospitalization. This is in keeping with our impression that hemoptysis occurs late in the natural history of lung cancer.

Figure 2 reveals the paradox by which the women who were hospitalized the most promptly had the shortest median survival. The same situation was noted by Boucot and Sokoloff[4] among Philadelphia survey-detected lung cancer cases. Perhaps only the most ill or those with the most rapid progression of symptoms were hospitalized promptly.

Delays in the hospitalization of undifferentiated carcinoma cases were of great length—one two years, one four, one five, and one seven years suggesting that, in this group of women, these tumors were surprisingly slow in growth. Table 9 shows delay in hospitalization according to tissue type.

Multiple Primary Cancers

Seven women had had non-pulmonary malignancies before the detection of their lung cancers. Table 10 lists these tumors with pertinent data. All tissue sections were reviewed by the respective hospital pathologist at the time of this study to confirm the conviction that these tumors had not been the primary sites of the pulmonary carcinomas.

TABLE 10—SEVEN CASES OF MULTIPLE PRIMARY MALIGNANT TUMORS IN WOMEN

Age	Race	Date of Previous Malignancy	Site of Previous Malignancy	Type of Cancer	Treatment	Date of Tissue Diagnosis of Lung Cancer	Tissue Type
59	W	1934	Breast	Ductal	Radical Mastectomy	1949	Squamous Cell
66	W	1935	Forehead (frontal area)	Basal cell	Deep x-ray	1949	Adeno-carcinoma
66	W	1944	Uterus	Adenocarcinoma	Panhysterectomy, bilateral salpingo-oophorectomy	1949	Squamous Cell
61	W	1945	Leg Hand	Epithelioma	Amputation Deep x-ray	1949	Undifferentiated
59	W	1947	Cervix	Squamous cell	Radium	1948	Adeno-carcinoma
57	W	1947	Uterus	Adenocarcinoma	Panhysterectomy, bilateral salpingo-oophorectomy	1949	Adeno-carcinoma
78	W	1948	Breast	Ductal	Radical Mastectomy	1950	Undifferentiated

Other Associated Conditions

Diabetes Mellitus: There were four diabetics among the 102 women. Two of them had squamous cell cancers, and two cancers of undifferentiated type. Their ages were 57, 61, 63, and 75 respectively. None survived five years. Jacobson,[18] in analyzing data from the National Health Survey, concluded that cancer was more prevalent than expected among diabetic white women over age 25.

Tuberculosis: One woman had concomitant active tuberculosis. A second woman in this study was treated for pulmonary tuberculosis for 18 months before the diagnosis of carcinoma was made. During this period all of the numerous sputa examined were negative for acid-fast bacilli.

Discussion

From this study of 102 women with histologically proved lung cancers, certain similarities and differences may be noted between lung cancer in women and in men. So far as age distribution, symptomatology and resectability are concerned, these women were quite like men in reported series.

Only one woman was asymptomatic suggesting that older asymptomatic women may not be x-rayed as frequently as older men or that, if radiologic abnormalities are found among them, the possibility of malignancy may not be suspected promptly. It is unfortunate that this study, undertaken five to eight years after diagnosis, yielded so few chest roentgenograms that a review of the films would not have been meaninful. It would have been interesting to contrast the appearance of chest roentgenograms at the time of diagnosis among these women with that of a matched sample of men with lung cancer.

The striking finding in our series as in Wynder et al's[13] study was the fact that only one-third of the cancers were of the squamous cell type. Squamous cell carcinoma constitutes 50 to 60 per cent of the lung cancers in reported surgical series,[7,14] preponderantly men. This seems reasonable if exogenous carcinogens or exogenous predisposing factors are involved in the causation of squamous cell cancer. Among the many suspect substances are three major categories—industrial materials like the chromates,[19] atmospheric pollutants such as 3-4 benzpyrene,[20,21] and tobacco smoke.[22]

Since few women work in the dusty trades, their exposure to industrial irritants or carcinogens is surely minimal. So far as atmospheric pollutants are concerned, the situation is not clear. Women certainly live in the same residential areas as men. While some speculate that women drive fewer miles than men and are apt to drive at times of less traffic, we know of no good data on this subject. If atmospheric pollution is a major factor in the increase in lung cancer, then, either women are less exposed to contaminated atmospheres or, to explain the marked differences in prevalence of lung cancer among them (1/100,000 for women and 69/100,000[4] for men) one must postulate that women have a special resistance factor. This might be genetic, hormonal, enzymal or even immunologic.

If tobacco smoke is a major factor in the causation of squamous cell lung cancer—whether as a primary carcinogen, a co-carcinogen, through bronchial irritation or through slowing of the ciliary stream, a marked increase in the incidence of lung cancer among women should soon occur. Haenszel, Shimkin and Mantel[23] report that male non-smokers have only slightly higher lung cancer mortality rates than female non-smokers. In the Philadelphia Pulmonary Neoplasm Research Project, lung cancer begins to assume major proportions only in relation to smokers who have smoked 40 years or more.[16] It was not socially acceptable for American women to smoke until some time after World War I. Therefore, it will be 1960 or later before any major effect due to smoking can be anticipated among women. Adequate data on smoking were not available on the women in this study. In the comparable study to be made on women diagnosed at the same hospitals during 1958 through 1960, smoking habits will probably be available on all cases. It will be of interest to note whether or not there will be an increased proportion of squamous cell carcinoma among women in the later study.

The 3 per cent five-year survival rate for the 102 women in this study is even poorer than such rates in most surgical series. Alton Ochsner[24] in a communication dated June 27, 1959, states that, in his overall series, the male-female ratio was 8.2:1 whereas, in the five-year survivors, it was 4.5:1. Possibly the poorer prognosis in our women was due to a low index of suspicion in regard to lung cancer when women have respiratory symptoms or abnormal chest films. It is unlikely that delay in seeking medical help is responsible since analyses of industrial sick absenteeism of men and women suggests that women are apt to consult physicians earlier than men. Another possibility is that the lung cancer fatality rate is higher for women than for men. Conceivably

the explanation would be the smaller proportion of squamous cell carcinoma among women since such cancers tend to be slower in growth and metastasis than other primary lung cancers. However, in this study, not one of the 26 women with squamous cell carcinoma lived two years. It is worth stressing that the three five-year survivors had completely normal bronchoscopic findings. The cytologic studies on their bronchial secretions were also normal. We have repeatedly found that the prognosis is grave when any bronchoscopic abnormality is found.[4,11]

Only one of the 102 women in this study had concomitant active tuberculosis. This is much lower than the 6 per cent tuberculosis rate among Philadelphia survey-detected lung cancer cases, predominantly men. The situation is not surprising since the tuberculosis problem today centers in older men, not in women in the cancer age.

SUMMARY

1. The five-year survival rate was 3 per cent for 102 lung cancer cases among women — all the proved cases that could be found at 43 Philadelphia hospitals for 1948 through 1950.

2. The resection rate was 27 per cent, about the same as that for men with lung cancer. Of the 34 women with normal gross bronchoscopic findings, one-half were resected, compared to only one-fifth of 43 with abnormal gross bronchoscopic findings.

3. Thirty-two of the cancers were undifferentiated, 30 were adenocarcinoma, 26 were squamous cell, and four terminal bronchiolar cell carcinoma in contrast to the usual predominance of squamous cell carcinoma among men.

4. There was only one asymptomatic patient in the series.

5. Seven per cent of the 102 women had a history of previous extrapulmonary malignancies; the lung cancer in each case was a second primary.

6. The prevalence rate of diabetes mellitus was 4 per cent and of concomitant proved active pulmonary tuberculosis was 1 per cent.

RESUMEN

1. Entre todos los casos de cáncer pulmonar comprobado que se encontraron en 43 hospitales de Filadelfia, hubo 102 en mujeres entre las que la sobrevida de 5 años, fué de tres por ciento en los años comprendidos de 1948 a 1950.

2. La proporción en que se hizo resección fué de 27 por ciento que aproximadamente es la misma que en los hombres con cáncer del pulmón. De las 34 mujeres con hallazgos macroscópicos normales a la broncoscopía, se resocaron los pulmones en la mitad de ellas, lo que es de compararse con un quinto de los 48 hombres en las mismas circunstancias.

3. Treinta y dos de los cánceres fueron indiferenciados, trienta adenocarcinomas, 26 de celdillas escamosas y cuatro bronquiolares terminales, lo que contrasta con el predominio habitual de los de celdillas escamosas en los hombres.

4. Sólo hubo un caso asintomático en esta serie.

5. Siete por ciento de 102 mujeres tuvieron antecedentes de malignidad extrapulmonar; el cáncer en cada uno de estos casos fué un segundo primitivo.

6. La prevalencia de la diabetes fué de 4 por ciento y de tuberculosis concomitante fué de 1 por ciento.

RESUMÉ

1. Le délai de survie a été de 5 ans pour 3% de 102 cas de cancer pulmonaire, constaté dans le sexe féminin — tous ceux qui purent être mis en évidence dans les 43 hôpitaux de Philadelphie de 1948 à 1950.

2. La proportion des exérèses fut de 27%, environ la même que celle pratiquée pour les hommes atteints de cancer pulmonaire. Sur les 34 femmes qui présentaient des constatations bronchoscopiques macroscopiquement normales, la moitié subit une résection, alors que cette intervention ne put être pratiquée que pour le 1/5 seulement de 43 cas présentant des constatations anormales à la bronchoscopie.

3. 32 cas de cancers étaient indifférenciés; 30 étaient des adénocarcinomes; 26 étaient des cancers épidermoïdes, et 4 étaient des carcinomes alvéolaires, contrastant la prédominance habituelle des épidermoïdes dans le sexe masculin.

4. Une seule malade de tout le groupe ne présentait aucun symptôme.

5. 7% des 102 femmes avaient des antécédents d'atteintes extrapulmonaires antérieures; dans chaque cas, la cancer pulmonaire était un cancer secondaire.

6. On constata un taux de 4% d'association avec le diabéte sucré et 1% de tuberculose pulmonaire évolutive associée.

ZUSAMMENFASSUNG

1. Die fünfjährige Überlebensrate lag bei 3% für 102 Fälle von Lungenkrebs bei Frauen; es handelt sich dabei um alle bestätigen Fälle, die in 43 Krankenhäusern von Philadelphia während der Zeit von 1948 bis 1950 ermittelt werden konnten.

2. Die Resektionshäufigkeit betrug 27%, also ungefähr die gleiche wie bei den Männern mit Lungencarzinom. Von den 34 Frauen mit normalen makroskopischen, bronchoskopischen Befunden wurden die Hälfte reseziert im Vergleich zu nur ein Fünftel von 43 Frauen mit pathologischen makroskopischen, bronchoskopischen Befunden.

3. 32 Krebsfälle waren histologisch undifferenziert. 30 waren Adenocarzinome, 26 waren Plattenzell— und 4 terminale bronchiolare Zellcarzinome im Gegensatz zu den üblichen Überwiegen von Plattenzellkrebsen bei Männern.

4. Unter diesem Krankengut befand sich nur ein Patient ohne Symptome.

5. Bei 7% der 102 Frauen waren in der Vorgeschichte bösartige Neubildungen außerhalb der Lungen vorausgegangen; der Lungenkrebs war aber in jedem Fall ein zeiter Primärtumor.

6. Das Vorkommen von Diabetes mellitus lag bei 4% und dasjenige einer gleichzeitig vorhandenen nachgewiesenen aktiven Lungentuberkulose bei 1%.

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The Immediate Effectiveness of Isoniazid Chemoprophylaxis as Determined by the Tuberculin Test*

A Five-Year Study Including 5,555 Navajo and Pueblo Children from Birth to 15 Years of Age and the Use of Isonicotinic Acid Hydrazide in the Prevention of Tuberculosis

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Animal experimentation has shown that isoniazid (INH) in the drinking water has a protective effect against tuberculous infection in guinea pigs.[1] There is also evidence that this drug will, in some instances, revert the tuberculin reaction to negative in children.[2,3,4] A large scale test of chemoprophylaxis has been carried out by the United States Public Health Service to determine the protection offered by INH against progressive and fatal forms of tuberculosis in infants and children.[5] To determine the ultimate effect upon endogenous reinfection and pulmonary tuberculosis such a test would require a follow-up period of over ten years.

Dr. Carl Gellenthien, Chairman of the Committee on Indian Affairs of the American College of Chest Physicians, conceived and originated controlled studies of the effect of INH in treating and preventing tuberculous infection of the Navajo and Pueblo Indian children of New Mexico. The Henry Phipps Institute of the University of Pennsylvania and the U. S. Bureau of Indian Affairs, now the Indian Health Division of the United States Public Health Service, combined their resources and completed this study June 30, 1959. The purpose of the study was confined to obtaining answers to two questions:

1) Would INH administered daily to children in the home and in school prevent tuberculosis infection as evidenced by the tuberculin test?

2) How regularly would INH so administered revert positive tuberculin test to negative?

The controls would furnish information as to the incidence of natural reversion of the tuberculin test to negative as previously observed by Dahlstrom.[6] It was hoped that subsequent follow-up of the controls and those "treated" might provide information as to the more remote effect upon the incidence and mortality of tuberculosis in the sample. It was also expected that such a field study could provide information as to the costs, feasibility and best methods of carrying out chemoprophylaxis on a wide scale.

A five-year study including 5,555 Navajo and Pueblo children from birth to 15 years of age and the use of isonicotine hydrazide in the treatment and prevention of tuberculosis.

*This project was sponsored by the Committee on Indian Affairs of the American College of Chest Physicians under the chairmanship of C. H. Gellenthien, M.D., Valmora, New Mexico. The field workers were: A. W. Dahlstrom, M.D., J. L. Wilson, M.D., who prepared this preliminary report, and Bretislav Sedlacek, M.D. The biostatistical collation and evaluation was done at the University of Pennsylvania.

**Deceased.

The Pueblo Indians of New Mexico were selected as the best available group for study, having had a tuberculosis survey in 1948 which showed tuberculosis infection rate among the school children of about forty per cent. To obtain a sufficiently large sample for statistical analysis the two Apache reservations in New Mexico and the Utes in the southwestern corner of Colorado were also included in the second year's tuberculin testing and distributing of pills.

Before the first tuberculin test and any administration in INH it was necessary to obtain the consent of the governors, tribal councils and parents in nineteen pueblos, five Indian schools and on two reservations of Ute and two reservations of Apache. This proved to be a long process involving much health education about tuberculosis. All of the 5,555 children to be included in the study, except the infants, had chest x-ray films by the mobile unit before the study. Any with x-ray film evidence of disease were excluded and hospitalized for treatment. Because of the time consumed in reaching all of the reservations extending from the Ute Mountain Utes down to the Mescalero Apaches it was necessary to divide the whole study into Group I consisting of 2,826 Pueblo Indians (and a few children in Navajo enclaves such as Alamo and Canoncito) first tested in 1955 and Group II, consisting of 2,729 Pueblo, Apache and Ute children, first tested in December 1956 and completed in 1958.

All tuberculin tests were done and read by Dr. Dahlstrom, until his death in August 1958, using platinum-iridium needles and .0001 mgm of PPD (Sharp and Dohme)=5TU. As soon as the children of Group I had been tested the pueblos involved were paired according to tribe population and infection rate as closely as possible. A coin was then tossed by a non-participant to determine which one of each pair of villages should receive only the placebo. The resulting key was filed in a sealed envelope and a copy sent to the pharmacist at the Indian Sanatorium in Albuquerque who used this as a guide in preparing the plastic vials of pills with names of villages and individual children on them. The Philadelphia office and the field staff did not know which villages received INH until a year of such administration had been completed and the code could be unsealed to stamp the cards either isoniazid or placebo. The treated and control groups were comparable as to age distribution and tuberculin reactions (see Chart A and Table 1). As some of the younger children had received BCG at birth in the hospital their cards were collated with the hospital birth records to add that information to x-ray film, tuberculin test readings in millimeters and other pertinent data.

To simplify distribution and encourage regular taking, INH was given in one daily dose calculated to furnish approximately from 5 to 10 mgm per kilo of body weight according to the following table:

Ages	Weight	Dose	Pills Daily
0-1 yrs.	4-10 kg.	50 mgm.	1
2-5 yrs.	10-20 kg.	100 mgm.	1
6-11 yrs.	20-40 kg.	200 mgm.	2
12-13 yrs.	45 plus	300 mgm.	3

The placebo was simply a tablet of lactose the same size and shape as the INH pill. Only when children moved to boarding school during the

study was there any opportunity for confusing medication and placebo or for comparative testing. No toxic effect was observed; one Zuni child had convulsions but turned out to be in the placebo treated group.

At the end of one year of administration of pills all the children in Group I had a tuberculin test and the results were tabulated. Those taking INH were continued on that medication for a second year and finally retested after stopping this prolonged treatment. The placebo was not continued for the second year in Group I because the double blind study was ended when the code was opened.

Included in Group II were several tribes with pairable reservations and the single large reservation of the Zunis. It was necessary to divide the Zunis by alphabetizing the surnames. In 1958 it became more difficult to follow the children in Group II as they were in many instances transferred to the public schools of New Mexico and Colorado. After the death of the Field Director, Dr. Dahlstrom, the testing of Group II was completed by Mrs. Edith P. Yeager, R.N., in October and November, 1958, within two months of the end of their year of treatment. Dr. B. Sedlacek, as Tuberculosis Control Officer of the Area Office, U. S. Public Health Service, was available to supervise the final testing of Group I.

Results

The results of the original tuberculin tests on the whole sample are shown in Table 1:

TABLE 1—REACTIONS TO FIRST TUBERCULIN TEST

Reaction	Size	Controls No.—per cent	On Isoniazid No.—per cent	Totals No.—per cent
Negative	0 mm.	2339—87	2191—85	4530—86
Doubtful	1-5 mm.	96— 3	66— 2.6	162— 3
Positive	6-10	52	90	142
	11-15	60	96	156
	16-20	76	88	164
	Over 20	64	46	110
Total Reactors:		252—10	320—12.4	572—11
Total Tests Completed		2687	2577	5264

In addition to those children who failed to return for a reading of their tests there were 453 "lost to program" in Group I in the first year including those missing from the first test or the final test. This dropping off was most marked among the infants (75 per cent) and preschool children (54 per cent). There were 748 in Group II who were lost to program because of an incomplete series of tests. There were 502 lost in Group I in the second year of its medication.

Protection against tuberculous infection is shown on Table 2.

TABLE 2—PREVENTION OF TUBERCULOUS INFECTION

	Controls		On Isoniazid		Totals
	No.	Conversion Rate	No.	Conversion Rate	
Non-Reactors	2339		2191		4530
Neg. to Pos. in 1 yr.	63	27 per M. per yr.	41	19 per M. per yr.	104

The low annual infection rate, (0.2 per cent per yr. in preschool children; 2.1 per cent per yr. for yrs. six to fourteen) markedly reduced since the survey of 1948, provided a relatively small sample of new reactors in the year of study. The difference between controls and INH treated children in rate of developing tuberculo-allergy was not great under the conditions of this study.

As shown in Table 4 the protection of Group I by INH was good for the first year, the infection rate being reduced to 7 per 1000 per year but the effect did not hold up well for a second year and the accumulative rate rose to 15 per 1000 per year.

The effect of daily administration of INH for a year upon positive tuberculin reactions is shown in Table 3.

TABLE 3—EFFECT UPON POSITIVE TUBERCULIN REACTIONS

	Controls		On Isoniazid		Totals
	No.	Reversion Rate	No.	Reversion Rate	
Reactors	252		320		572
Reversions Pos. to Neg.	9	36 per M. per yr.	48	150 per M. per yr.	57
Change in Total Diam.		plus 566 mm.		minus 215 mm.	
Remained Positive Average Diameter		14.9 to 17.1 mm.		12.4 to 11.6 mm.	

Reversion from positive (over 5 mm. of induration) to negative occurred at a rate almost five times as great as among the controls. While it is true that most reversions to negativity were from levels of allergy producing reactions from 6 to 10 mm. in diameter, 20 of the 48 occurred from original reactions over 10 mm. in diameter.

This small series also showed that there was a normal reversion rate of about 36 per 1000 reactors a year under the conditions in which these children lived and also that 6 of these 10 natural reversions occurred in strong reactors originally.

To avoid any judgment as to whether reactions were positive or doubtful and to determine the total effect of INH the diameter of all reactions which were measurable at the beginning and the end of the year of medication were totalled for both controls and INH groups to obtain total direction and amount of change and averages shown on Table 3.

TABLE 4—EFFECTS OF 2 YEARS OF ISONIAZID

	At Start No.	End of 1st yr. No.	End of 1st yr. Rate	End of 2nd yr. No.	End of 2nd yr. Rate	Total
Negative	1189	846		568		
Doubtful	33	—		—		
Neg. to Pos.	—	8		17		25
Infection Rate	—		6.7 per M per yr.		15 per M per yr.	
Positive	178	98		78		
Pos. to Neg.	—	45		12		57
Reversion Rate	—		253 per M per yr.		160 per M per yr.	
Lost to Program	—	403		502		
Totals	1400	1400		1177		

This demonstrates that reversion to negativity is merely a part of a general effect of INH in reducing tuberculo-allergy.

The reversion rate among the children in Group I who took two years of INH daily was much greater the first year (253 per 1000 reactors per yr.) than in the second year with an annual rate from 57 accumulative reversions of 160, very little greater than the rate, 150, for the whole sample treated for 1 year. (See Tables 3 and 4).

Protection from active tuberculosis cannot be reported at this time because follow-up chest x-ray films have not been completed. None of the children under treatment or of the children on the placebo developed clinical signs of meningitis or acute tuberculosis during the study.

It is believed than an annual follow-up with x-ray films and study of hospital admissions and deaths will be necessary to provide information about the ultimate effects of this prophylactic therapy upon the tuberculous rates among the Indian children.

No conclusion is justified until the biostatistical analysis of the data is completed. However it may be inferred now that: (1) It is safe to administrate INH to children in the dosage used daily for as long as two years.

(2) INH will greatly increase the rate of reversion of the tuberculin reaction to negative.

(3) INH is not particularly effective in protecting a large and scattered population of children against tuberculous infection.

(4) The ultimate effect upon immunity and resistance to tuberculous disease is still to be determined.

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Ivalon Sponge Prosthesis with Pulmonary Resections Over Five Years Experience

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Ever since the beginning and acceptance of pulmonary resection as a procedure, surgeons have tried to find better ways of dealing with the residual empty space. The importance of getting rid of this space as rapidly as possible is well recognized. With lobectomy or partial resection, immediate obliteration seems to definitely reduce the incidence of complications such as persistent air leaks, and bronchial fistulae. This has been accomplished in various ways such as: (1) by division of the pulmonary ligament which allows the lower lobes and segments to rise in the chest cavity; (2) by crushing or cutting the phrenic nerve, thus elevating the diaphragm (not too desirable after lobectomy because of interference with the cough mechanism; (3) induction of pneumoperitoneum, temporarily elevating the diaphragm; (4) the development of some type of so-called apical pleural tent; and (5) thoracoplasty. All of the temporary procedures are helpful, particularly during the immediate postoperative period; however, sooner or later their efficacy wears off and the residual lung begins to over-distend. This raises a new problem regarding a decrease in function of the remaining over-distended segments. Concomitant, pre-resection, and early post-resection thoracoplasty, being permanent collapse procedures, solve this point, but have the disadvantage of the accompanying deformity, and in some instances multiple operations. The pre-resection extra-periosteal plombage operation also has been used with satisfaction, eliminating resection of ribs.

Following total pneumonectomy, obliteration of the space becomes even more important. Over-distention of the one remaining lung definitely limits exercise tolerance, and, in an individual who already has emphysema or much fibrosis due to disease in the contralateral lung, will cause him to be a pulmonary cripple. A young individual can get by for many years with pneumonectomy alone, but eventually will find it necessary to slow down his activity. With some older individuals who do not have emphysema, resection alone, as for carcinoma, may be tolerated very well for a short life period. If emphysema or pulmonary fibrosis is present, the residual space had better be taken care of in some manner. Also, obliteration of the space should be by some permanent procedure. Here again, phrenic crush, pre and post-resection, and concomitant thoracoplasties have proved their value.

Since the beginning of this century, surgeons have tried a multitude of various and foreign substances to fill body cavities and to maintain a collapse of the lung. Air, fat, muscle, oil, cellophane, rubber, paraffin, fiber glass, metal, and recently the plastic substances, all have been used. Some have been discarded and revived again. In the words of J. C. Trent, "The search for the ideal substance goes on." Two scores of articles in American and foreign literature written about these substances in the last fifteen years were reviewed and no final conclusion could be reached

regarding the value of plastic sponges, balls, paraffin, or some of the other supposedly inert substances used to fill spaces in the chest. All were condemned by some and praised by others. There was no uniformity of terminology to help evaluate the different procedures. The word "prosthesis" (a space filler) was confused with "plombage" (a collapse procedure). In a number of articles, it was even neglected to mention whether the substance was placed extrapleurally, extraperiosteally, or within the pleura. Empirical opinions were predominant, many based on as few as two to a dozen examples. In general, the literature was confusing, to say the least.

This study was designed with hopes of dispelling some of the doubts and not adding to the confusion of what happens to patients with a particular foreign substance inserted into the chest cavity over a period of years—in this instance the Ivalon Sponge.* In all the cases of this series, the sponge was used as a *Prosthesis* to fill the space caused by partial or total resection of the lung. Forty-three instances in which the Ivalon sponge was used with a collapse or *plombage* procedure have been reported elsewhere.[1] This report deals with 111 cases operated upon in the five and one-half years between October, 1953 and April, 1959.

TABLE 1—OF THE 87 CASES STILL LIVING, SPONGES HAVE BEEN IN PLACE OVER:

5 years	in 22 cases.
4 years	in 12 cases.
3 years	in 14 cases.
2 years	in 9 cases.
1 year	in 30 cases.

Of the total 111, 87 are living and 24 are dead. Of the living, 22 have had the sponges in place over five years, twelve over four years, 14 over three years, nine over two years, and 30 over one year. A total of eleven (10 per cent) of the sponges have become infected to date.

*Ivalon Sponge is distributed by Clay-Adams, Inc., New York, N. Y.

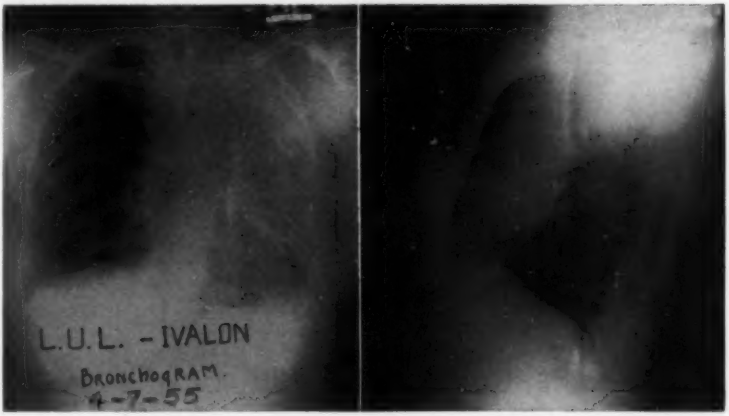

FIGURE 1A FIGURE 1B

FIGURE 1A (Case 1): Illustrates an intrapleurally located sponge following a left upper lobectomy. Bronchogram outlines left lower lobe. 1B: (Case 1), Lateral view.

TABLE 2—TYPES OF CASES IN WHICH SPONGE WAS USED

Tuberculosis	76
Cancer	31
Post-radiation fibrosis (breast)	1
Adenoma and suppuration	1
Putrid lung abscess	1
Benign tumor	1

Seventy-six of the operations were performed on tuberculosis patients, 71 of whom are still alive; 31 for cancer of the lung, 12 are still alive; one each for post-radiation fibrosis of the lung, suppurative disease with bronchial adenoma, putrid abscess of the lung, and last for a benign polypoid xanthofibroma of the bronchus—all of whom are living.

There were four of the 24 deaths classified as being within the post-operative period. One of these cases was re-explored for persistent bleeding and died of ventricular tachycardia. The other three died one, three, and fourteen days post-operatively, all from coronary occlusion proved by autopsy. Two of these were in cancer cases.

TABLE 3—CASES HAVING TOTAL PNEUMONECTOMY AND IVALON PROSTHESIS

Cancer		27	
Tuberculosis		55	
Miscellaneous		4	
Total		86	
Intrapleural	85	Extraperiosteal	1

In 86 cases, the sponge was used in conjunction with total pneumonectomy—27 in cancer, 55 in tuberculosis, and the four miscellaneous cases. All these sponges were inserted at the time of the resection, and in all but one, the sponge was placed directly in the pleural cavity. In one case, the pleura and the periosteum was reflected and the sponge inserted extraperiosteally.

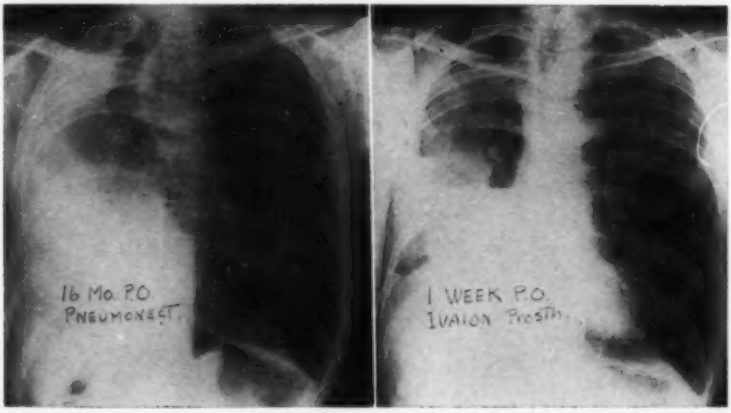

FIGURE 2A FIGURE 2B

FIGURE 2A (Case 2): Shows mediastinal shift 16 months after a simple right total pneumonectomy for carcinoma. 2B (Case 2), Shift corrected by post-pneumonectomy Ivalon prosthesis.

TABLE 4—CASES HAVING LOBECTOMY AND IVALON PROSTHESIS

Tuberculosis		17	
Cancer		2	
Total		19	
Intrapleural	7	Extraperiosteal	12

In 19 cases, the sponge was used concomitant with lobectomy, two for cancer, and 17 for tuberculosis. In seven of these, the Ivalon was placed directly in the pleural cavity (Case 1, Figs. 1A, 1B), and in 12 it was inserted in an extraperiosteal location. These last are reported in detail in another article.[3] In the latter instance, lobectomy is done first, following which an extraperiosteal space is developed in a similar manner as with the usual extraperiosteal plombage procedure, the sponge is then inserted and the chest wall closed. In six cases, the sponge was used as a post-pneumonectomy prosthesis. Occasionally, one sees a patient who has had total pneumonectomy some time previously and who has developed a marked shift of the trachea and esophagus resulting in difficulties in swallowing, marked wheezing and respiratory distress, especially accompanying periods of colds and bronchitis. Because of the mediastinal shift, (seen most often with left pneumonectomy) the heart may be turned on its long axis, giving rise to palpitation, irregularities of rhythm

TABLE 5—NUMBER OF MONTHS AFTER PNEUMONECTOMY THAT POST PNEUMONECTOMY PROSTHESIS WAS INSERTED. TOTAL SIX CASES.

5 months.
7 months.
10 months.
16 months.
24 months.
45 months.

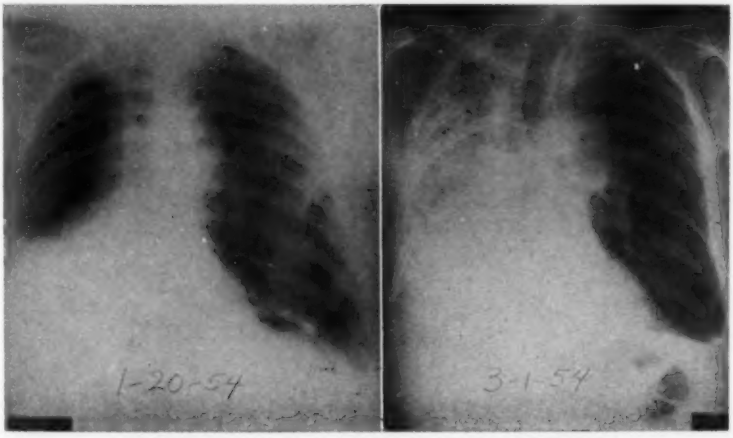

FIGURE 3A FIGURE 3B

FIGURE 3A (Case 3): Demonstrates a huge pneumatocele originating from the left upper lobe and invading the empty right pleural cavity 3½ years after a right total pneumonectomy for carcinoma. There is also a co-existing spontaneous pneumothorax collapse of the left lung. 3B (Case 3), After re-expansion of the left lung, removal of the pneumatocele and insertion of an Ivalon prosthesis into the right pleural cavity.

and angina-like pains. In such a situation, dramatic relief is afforded by performing a post-resection thoracoplasty.

The Ivalon sponge was used as a post-pneumonectomy prosthesis instead of doing thoracoplasty in six such instances (Case 2, Figs. 2A, 2B). These sponges were inserted five, seven, 10, 16, 24, and 45 months following pneumonectomy. In four of these instances, it was placed in the pleural cavity, and in two in an extraperiosteal location. One of these cases was most interesting (Case 3, Figs. 3A, 3B). It was one of the early prostheses, being the sixth in this series, operated upon in February of 1954. Right total pneumonectomy was performed for squamous cell carcinoma on May 28, 1950. In the course of the following year, a huge pneumatocele developed in the apex of the left lung, crossed the anterior mediastinum and completely filled the right chest cavity. On three occasions in January of 1954, this patient developed spontaneous tension pneumothorax collapse of the left lung—treated each time by insertion of a catheter and suction. On February 24, 1954, the right chest was reopened, a huge cyst was mobilized, dissected across the anterior mediastinum, and severed at its base in the left upper lobe. The right chest space was then filled with an Ivalon sponge to prevent any further herniation. This patient is alive and well to this date, has had his sponge in place over five years, and is in his 10th year after an operation for carcinoma.

Three patients in the series had planned pre-resection thoracoplasties; however, after the first stage rib resection was done, pneumonectomy was performed and an intrapleural sponge was inserted to fill the remaining space rather than removing more ribs. Two patients had pre-resection, extraperiosteal Ivalon sponge plombage operations. Resections were performed later below the plombage and a second sponge placed intrapleurally to fill the remaining space (Case 4, Figs. 4A, 4B). One patient

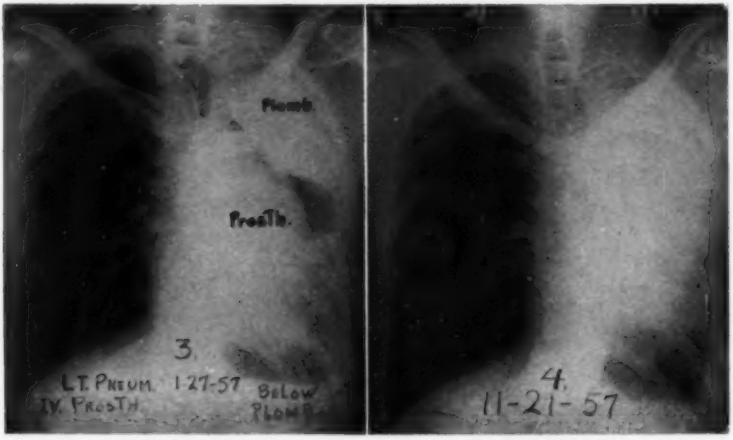

FIGURE 4A FIGURE 4B

FIGURE 4A (Case 4): Illustrates a pre-resection extraperiosteal plombage following which a left total pneumonectomy was performed below the plombage and a second sponge placed intrapleurally as a space filler. 4B (Case 4), Eleven months later after absorbtion of the residual air around the prosthesis.

has had an upper lobe resected on each side with concomitant, extraperiosteal Ivalon prosthesis. Two have had thoracoplasties on one side and lobectomy with concomitant, extraperiosteal prosthesis on the contralateral side.

Infection of the sponge was the only serious complication noted in this series of cases. There were 11 infections in the 111 cases (10 per cent) Rapid and sometimes excessive accumulation of bloody serum was noted in some cases, however, not any more frequently than usually seen associated with an ordinary pneumonectomy. Nevertheless, it is quite important to watch for excessive fluid accumulation from the second to the 14th post-operative day. If there is a great deal of entrapped air or fluid that seems to be causing a shift of the mediastinal structures to the opposite side, it should immediately be removed by aspirating the chest with a 50 cc. syringe, three-way stop cock, and a 16 gauge needle. In rare cases, this might mean aspirating as often as every other day for a week or two. If pressure by excessive fluid is allowed to build up within the chest, besides interfering with respiration and the cough reflex, it is apt to break through the wound. In such cases, infection of the sponge is inevitable, as happened in one of our cases. When there is x-ray evidence of negative pressure in the chest, no shift of the mediastinum to the opposite side and no depression of the diaphragm, even though a moderate amount of air or a fluid level is present, the case should be left alone and not tapped.

Following pneumonectomy, the sponge is placed directly within the pleural cavity. An attempt is then made to create negative pressure in the space by removing all the air possible. After closing, one can aspirate much of it with a needle and syringe. Usually, however, the end of a No. 14 or No. 16 catheter is left in the pleural space and the wound closed tightly about it. After suturing the skin, and just before removing the catheter, the open end of it is placed in a pan of water. Pressure on the

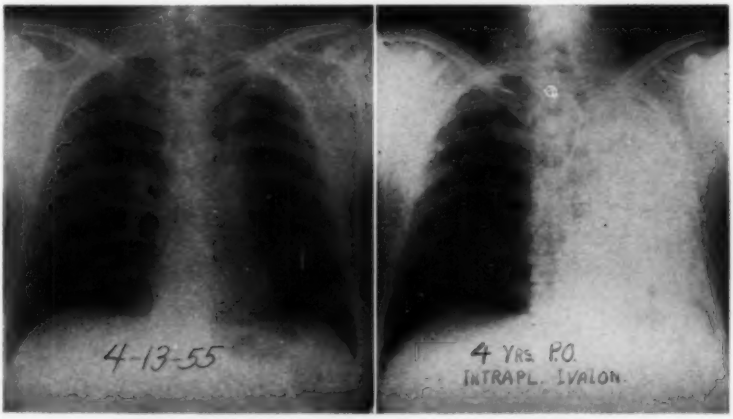

FIGURE 5A FIGURE 5B

FIGURE 5A (Case 5): Pre-operative film illustrating a large benign polypoid xanthofibroma of the left main bronchus. 5B (Case 5), Film taken four years after left total pneumonectomy and intrapleural Ivalon prosthesis which became infected. Ivalon sponge is still in the left pleural cavity. Patient is well.

bag by the anesthesiologist will inflate the remaining lung and deflect the mediastinum towards the operative side. Along with this, the surgeon, by contracting the chest wall with his hands, will force most of the air from the operated side bubbling it through the water. The catheter is then removed. The same thing has been accomplished by leaving the catheter in place and applying active under-water suction for 24 hours.

Eleven infections occurred in the 111 cases of this series. In an attempt to determine the cause of these infections, the 11 cases were found roughly to fall into three groups with respect to the time following surgery that first signs of infection appeared.

TABLE 6—GROUP I INFECTIONS

Disease	Oper.	Inf. Appeared	Culture	B.P. Fist.	Cause
Tbc.	Total pn.	3 weeks	Staph.	No	Cavity ruptured during surgery.
Tbc.	Total pn.	3 weeks	Pn. & Strep.	No	Cavity ruptured during surgery.
Tumor	Total pn.	3 weeks	Staph.	No	Possible contam. during surgery.

Group I, or the early cases, all appeared three weeks after operation. None of these had evidence of bronchopleural fistula. In two, cavities were ruptured during surgery, thus causing contamination of the pleural cavities. The third case was also quite likely contaminated at the time of surgery.

In Group II, or the medium cases, the infection appeared between one and nine months after surgery. All of these had bronchopleural fistulae which obviously caused infection of the sponge. It hardly seems likely

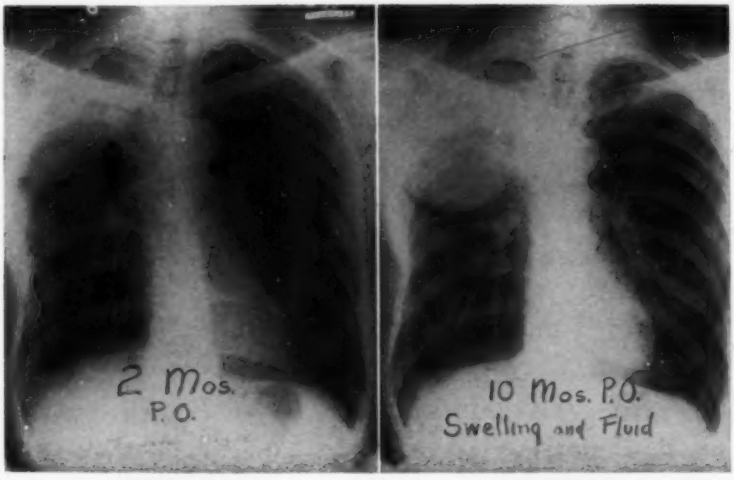

FIGURE 6A FIGURE 6B

FIGURE 6A (Case 6): Film taken two months after right upper lobectomy and intrapleural Ivalon prosthesis. 6B (Case 6), Demonstrates swelling of the sponge ten months later indicating infection.

TABLE 7—GROUP II INFECTIONS

Disease	Oper.	Inf. Appeared	Culture	B.P. Fist.
Tbc.	Total pn.	1 mon.	Negative	Yes
Tbc.	Total pn.	2 mos.	Staph.	Yes
Tbc.	Lobectomy	5 mos.	Gm. Neg. bac.	Yes
Tbc.	Total pn.	7 mos.	Negative	Yes
Tbc.	Total pn.	9 mos.	Staph.	Yes

that the sponge itself would be the cause of a fistula in only five of the 111 cases.

TABLE 8—GROUP III INFECTIONS

Disease	Oper.	Inf. Appeared	Culture	B.P. Fist.	Cause
Tbc.	Total pn.	12 mos.	A.F.B.	No	Acute exacerbation of disease.
Cancer	Lobectomy	19 mos.	Negative	No	Hist. of acute resp. inf. 6 weeks before.
Cancer	Total pn.	40 mos.	Staph.	No	Hist. of acute resp. inf. 3 weeks before.

Group III, the late cases, are much harder to explain. None of these had bronchopleural fistulae. One of these was the only case in which acid fast bacilli were cultured from the sponge. It is possible that this sponge was infected through the lymphatic route. Since there was no bronchial fistula, the patient was drug resistant and had considerable pre-existing disease in the contralateral lung, the evidence points in favor of the sponge being the recipient of infection rather than the cause of exacerbation. In the two other late cases, no explanation of the infection could be determined other than that in both instances there was

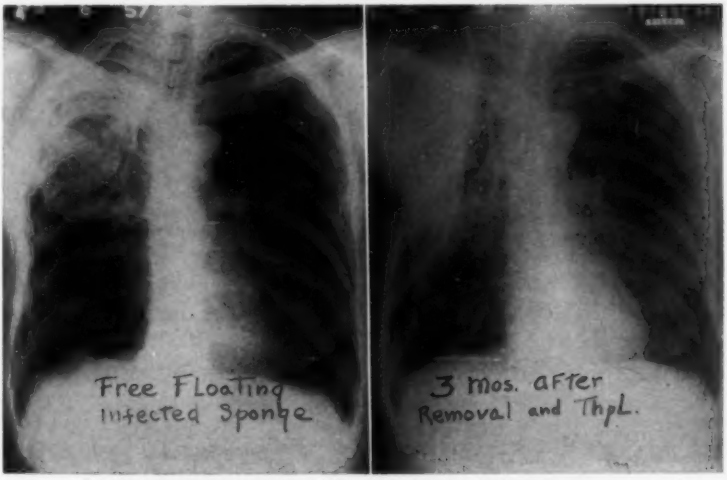

FIGURE 6C FIGURE 6D

FIGURE 6C (Case 6): After aspiration of the purulent exudate showing air around the floating sponge. 6D (Case 6), Three months after removal of the infected sponge and tailoring thoracoplasty.

history of rather severe respiratory infection and pneumonia one to three months before appearance of symptoms of trouble with the sponge. Here, again, arises the question of the possibility that the sponge might become infected by way of the lymphatics or blood stream. Remember also that the last two cases were cancer subjects and neither had evidence of bronchopleural fistula.

As determined by this series of cases, factors that might cause infection of the sponge are: (1) primarily, the development of bronchopleural fistula; (2) contamination at the time of surgery by rupturing into cavities, empyema pockets, or other errors in surgical technique; (3) possibility of infecting the sponge through the lymphatics or blood stream; and (4) insufficient washing, or improper sterilization of the sponge.

Infections of the sponge occurred in eight of the 76 tuberculosis cases (10 per cent), two of the 31 cancer cases (6 per cent), and one benign tumor case. The last case was the only infected case in which the sponge was not removed. Cultures in this case revealed staphlococcus aureus and this sponge was apparently sterilized by repeated aspiration and instillation of antibiotics. The sponge is still in the chest and the patient is alive and well four and one-half years following occurrence of the infection (Case 5, Figs. 5A, 5B). In nine of the 10 cases in which the infected sponge was removed, concomitant thoracoplasty was performed. In one only, the sponge was removed and no thoracoplasty was performed. Ten of the 11 infected cases are still living and well. One of the infected tuberculosis cases died two and one-half years after the sponge was removed. Cause of death in this case was cancer of the bladder with metastases. Nine of the infected cases followed total pneumonectomy and two followed lobectomy. Of the 11 infected cases, cultures of the sponge were negative in three, one showed streptococci and pneumococci, one demonstrated a gram negative bacillus, five showed staphlococci, and only one of the eight tuberculosis cases had positive tuberculosis culture of the infected sponge. Of interest, also, was the fact that of the 76 tuberculosis cases operated upon, 18 were drug resistant and had positive sputum at the time of surgery. In spite of this risky situation, only three of these (16 per cent) were in the infected group.

At this point it should be mentioned that it is a simple matter to remove an infected sponge (Case 6, Figs. 6, 6A,B,C,D). Most of the time it is found floating freely in the purulent exudate and can be merely plucked out of the chest. Performing a concomitant thoracoplasty is also no difficult task. The pleural cavity is usually drained for a week or two following removal of a sponge. (Fig. 7 is a microphotograph of an infected sponge, and Fig. 8 shows a sponge that has been in place 19 months, removed at autopsy from a patient who died of diabetes and uremia.)

Something might be mentioned here about a certain technique favored in bronchial closure. For the past several years, one of us (J.E.D.) has routinely been closing the bronchial stump with many fine wire sutures placed over the end and, in some cases, then using a method of covering the stump with a portion of muscle taken from the chest wall. The piece of muscle is held in place by means of two mattress sutures of No. 4-0

cotton carefully placed on each side of the stump. After first inserting the sutures, the muscle is slid down the cotton and they are then tied. This results in a thick pad over the bronchial stump covering the sharp ends of the wire sutures and preventing injury to neighboring vessels by the cut wires. This also creates a heavy layer of scar tissue over the stump which might help reduce the incidence of broncho-pleural fistula.

Washing and sterilization of the sponge before use is of the greatest importance. It is believed that improper preparation of the material has resulted in the unfortunate experiences reported by some others. Formaldehyde used by the manufacturer for preservation of the sponge must be thoroughly removed before use. The sponge must be thoroughly washed a full 30 minutes in running water. It should then be completely immersed in water in a large container and boiled for another 30 minutes or sterilized in the autoclave. Nothing must touch or compress the sponge

Figure 7

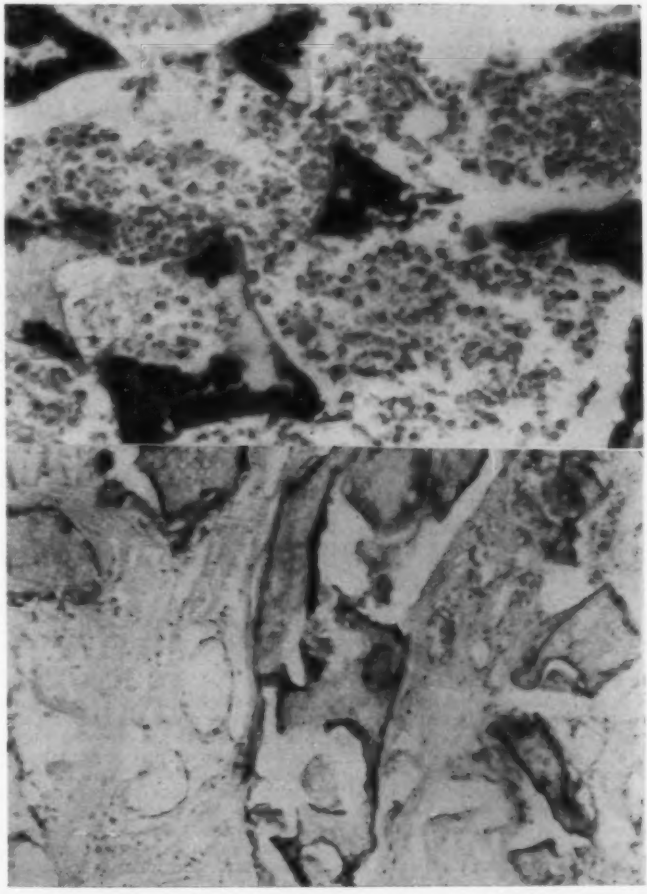

Figure 8

FIGURE 7: Microfilm showing the purulent exudate in an infected sponge. FIGURE 8: Microfilm shows absence of inflammatory or foreign body reaction in a sponge at autopsy nineteen months after insertion following pneumonectomy. Cut was taken adjacent to the surface.

before it is completely cooled or it will lose its shape. Several such washings and sterilizations will do no harm. After cooling, at the operating table, it can easily be sculptured with scalpel or scissors to fit the space. One to two million units of penicillin, and one to two grams of streptomycin in 60 ml. of saline are placed in the sponge, particularly near the bronchial stump, at the time of insertion.

SUMMARY

Observations of five and one-half years on a series of 111 cases in which the Ivalon sponge was used as a prosthesis or space filler with pulmonary resection was reported.

Eleven, (10 per cent) of the cases became infected. These were broken down into three groups, early, medium, and late, and an attempt made to analyze the cause of the infections. Points of technique were discussed and a new way of covering the bronchial stump with a free muscle graft was suggested. This report has been presented, not so much with the idea of recommending a procedure for common use, but as the attempt to ascertain true facts about what would actually happen to a large group of cases in which a specific foreign substance has been inserted in the chest cavity over a long period of time. It is obvious that there would be many instances of disaster should any of the techniques discussed come to widespread and general use. However, the principal reason for trouble occurring would be careless and indiscriminate use of the sponge in situations where infection might naturally occur, such as when cavities or localized empyema spaces are ruptured, or when generalized or overwhelming infection is present.

Lastly, it stands to reason that the incidence of infected sponges ought to parallel the incidence of bronchopleural fistula that occurs with each individual surgeon's group of resected cases.

RESUMEN

Se relata el resultado de la observación durante cinco años y medio de una serie de 111 casos en los que se usó la esponja de Ivalon como prótesis o relleno del especio después de resección pulmonar.

Once (10 por ciento) de los casos se infectaron. Se dividieron éstos en tres grupos: tempranos, medios y tardíos, y se intentó analizar la causa de la infecciones. Se discutieron detalles técnicos y se sugirió una nueva técnica de cubrir el muñón bronquial con injerto muscular libre. Este informe se ha presentado no tanto para recomendar el procedimiento para uso común, sino como intento para descubrir hechos verdaderos acerca de lo que realmente ocurre en un gran número de casos en los que se ha insertado un cuerpo extraño determinado en el tórax por un tiempo largo. Es claro que habría muchos casos desastrosos si la técnica descrita se generalizara ampliamente.

Sin embargo, la causa principal de complicaciones sería el uso indiscriminado y descuidado de la esponja cuando es de esperarse que la infección ocurra de manera natural como cuando ha habido ruptura de cavernas o de empiemas localizados o cuando hay infección general dominante.

Por último es razonable sostener que la incidencia de las esponjas infectadas debe ser paralela a la de las fístulas bronchopleurales que ocurren en cada grupo individual de los casos que cada cirujano reseque.

RESUMÉ

Les auteurs rapportent leurs observations portant sur cinq ans et demi et concernant 111 cas pour lesquels une éponge d'Ivalon fut utilisée comme prothèse ou pour combler l'espace lors d'une résection pulmonaire.

11 de ces cas (10%) s'infectèrent. Ils sont séparés en trois groupes: précoce, moyen et tardif et les auteurs essayent d'analyser la cause de l'infection. Des points de technique sont discutés et les auteurs évoquent un nouveau moyen de recouvrir le moignon bronchique avec une greffe de muscle. Cette communication a été présentée, pas tellement dans l'idée de recommander un procédé d'emploi courant, mais comme une tentative pour découvrir des faits vrais lorsqu'une substance étrangère spécifique a été installée dans la cavité thoracique pendant une longue période de temps. Il est évident qu'il devrait y avoir beaucoup d'exemples d'accidents si chacune des techniques discutées venait à être diffusée et entrait dans la pratique courante. Cependant la raison principale des troubles serait l'utilisation indiscriminée et sans soin de l'éponge dans des états où l'infection pourrait survenir naturellement, tels que lorsque des cavités ou des espaces d'épanchement localisé sont rompus ou lorsqu'il existe une infection généralisée ou latente.

Enfin, il tombe sous le sens que la fréquence des infections survenant sur les éponges devrait être mise en comparaison avec la fréquence des fistules bronchopleurales qui surviennent dans tout groupe chirurgical de résections.

ZUSAMMENFASSUNG

Es handelt sich um einen Bericht über 5½-jährige Beobachtungen an einer Reihe von 111 Fällen, bei denen ein Ivalon-Schwamm als Prothese bzw. Füllmaße bei Lungenresektionen zur Anwendung kam.

In 11 Fällen (10%) trat eine Infektion ein. Diese werden in drei Gruppen aufgeteilt: früh, mittel und spät; und es wird ein Versuch unternommen, die Ursache der Infektionen zu analysieren. Probleme der Operationstechnik werden diskutiert und ein neues Verfahren zur Deckung des Bronchialstumpfes mit einem freien Muskeltransplantat vorgeschlagen. Dieser Bericht wurde vorgelegt-nicht so sehr mit der Vorstellung, ein zur allgemeinen Anwendung geeignetes Verfahren zu empfehlen-als vielmehr im Sinne eines Versuches zur Ermittlung des wahren Sachverhaltes hinsichtlich dessen, was zur Zeit bei einer großen Gruppe von Fällen geschieht, bei denen ein spezieller Fremdkörper für einen langen Zeitabschnitt in die Brusthöhle eingebracht wurde. Es liegt auf der Hand, daß oft genug Unheil eintreten würde, wenn eines der besprochenen Verfahren zur weit verbreiteter, allgemeiner Anwendung käme.

Die Hauptursache für das Auftreten von Zwischenfällen würde jedoch im einem fahrlässigen und wahllosen Gebrauch des Schwammes in Situationen bestehen, in denen es schon von sich aus zur Infektion kommen kann, d.h. bei Cavernenruptur oder Eröffnung von lokalisierten Empyem-Resthöhlen, oder wenn eine allgemeine oder übermässig schwere Infektion besteht.

Schliesslich versteht sich von selbst, daß die Häufigkeit infizierter Schwämme parallel gehen muß mit der Häufigkeit von bronchopleuralen Fisteln, die im Resektionsmaterial einer jeden Chirurgengruppe vorhanden sind.

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Causes of Death and Pathologic Findings in 304 Cases of Bronchial Asthma*,**

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There is a widespread impression that bronchial asthma seldom causes death. This study shows clearly that the disease terminates fatally more often than is generally thought.

This paper summarizes the data obtained in a review of all cases in which the clinical diagnosis of bronchial asthma was made at the Mayo Clinic during the 40-year period 1916 through 1955 and in which necropsy was performed. The series totals 304 cases, and is the largest reported so far.

Incidence of Bronchial Asthma

Other than stating that the disease is frequent, the literature lacks information as to how common asthma is. The following data provide additional information as to the occurrence of the disease. During the year 1955, a diagnosis of bronchial asthma was made in 1667 of the

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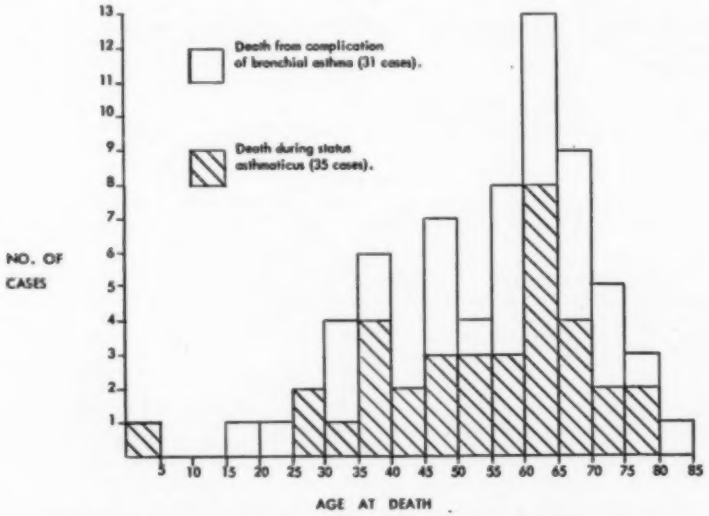

FIGURE 1: Age of patients at death in fatal bronchial asthma.

119,000 patients who registered at the Mayo Clinic, giving an incidence of 1.4 per cent. The estimated incidence for 1954 was 1.3 per cent.

Of 743 known deaths occurring among all clinic patients seen during 1955, 25 (3.4 per cent) were among asthmatic patients. Four of the 25 patients died in status asthmaticus, two from complications of asthma (emphysema and cor pulmonale), and the remaining 19 from causes unrelated to asthma. Thus, 1.5 per cent of the 1667 asthmatic patients seen during 1955 died in that year.

Duration of Bronchial Asthma

The age at the time of death from status asthmaticus (group A) varied from 5 to 78 years (Fig. 1). Thirty-seven per cent of the patients in this group died before and 63 per cent during or after the age of 51 years. More than 50 per cent died in the age period 51 through 70 years.

The range in age at the time of death among patients dying from a complication of bronchial asthma other than status asthmaticus (group B) was very similar to the range for those with status asthmaticus.

Seventeen of the patients in group A were female and 18 were male. In group B, nine of the patients were female and 22 were male.

The duration of bronchial asthma in years before death varied from 1 to 66 years (Fig. 2). Of the patients dying of status asthmaticus, 20 per cent died within 5 years after the onset of asthmatic symptoms, 45.7 per cent within 10 years, 65.7 per cent within 20 years and 82.9 per cent within 30 years.

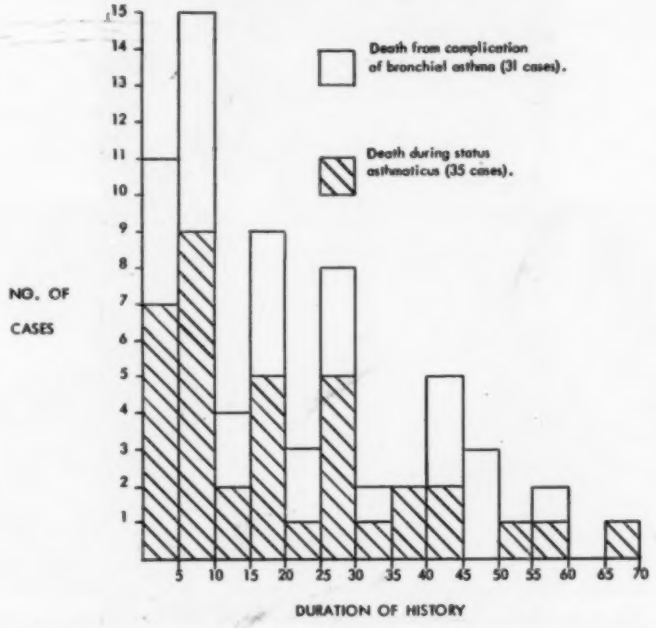

FIGURE 2: Duration of history of bronchial asthma in years at death.

Of the deaths due to a complication of bronchial asthma other than status asthmaticus, 12.9 per cent occurred within 5 years after the onset of asthma, 32.2 per cent within 10 years, 51.6 per cent within 20 years and 67.7 per cent within 30 years.

Causes of Death in 304 Asthmatic Patients

During the 40-year period 1916 through 1955, there were 450 known deaths among clinic patients having had a diagnosis of "asthma" made sometime during their clinic visits. Seventy-seven of these cases were rejected from this study because necropsy had not been performed. An additional 69 cases were rejected because examination of the clinical records revealed a vague or equivocal history of bronchial asthma, or a diagnosis of "cardiac asthma."

The remaining 304 cases were divided into three groups, as shown in table 1. Four patients in group A and three in group B died soon after receiving 1/6 to 1/4 grain of morphine sulfate. Among the causes of death in group B were bronchiectasis, bronchopneumonia and emphy-

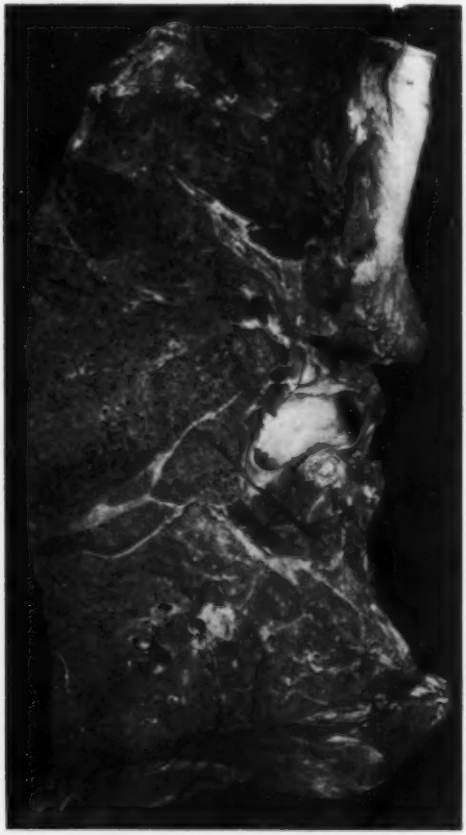

FIGURE 3: Lung showing bronchiectasis with emphysema.

TABLE 1—CAUSES OF DEATH (1916-1955) AMONG ASTHMATIC PATIENTS ON THE BASIS OF NECROPSY DATA

Group	Patients	Per cent
A. Death during status asthmaticus	35	11.5
B. Death from complications of asthma	31	10.2
C. Death unrelated to bronchial asthma	238	78.3
Total	304	100.0

sema. Two patients died during bronchoscopic examination and one died immediately after receiving a parenteral injection of penicillin.

Data on the causes of death in group C are given in Table 2. Cardiovascular and malignant disease accounted for approximately 60 per cent of the deaths in this group. Carcinoma of the lung was the most common malignant condition; it represented 34 per cent of the deaths from malignant disease in males. Cerebrovascular, renal and postoperative deaths were much less common. The incidence of suicide should be noted.

Gross Findings in Groups A and B (Deaths From Status Asthmaticus or Complications Thereof)

Gross emphysema (Fig. 3) was common in both groups. It was found in all but one (97.1 per cent) of the cases of status asthmaticus (group A), and in 52 per cent it was marked. It occurred in 81 per cent of the cases in which death resulted from some complication of bronchial asthma other than status asthmaticus (group B). The bronchial walls were thickened in 40 per cent of the cases in group A, and in 29 per cent of those in group B. Pulmonary edema was found in approximately one-fourth of the cases in each group.

Hydrothorax and pleural adhesions were each nearly twice as frequent in group A as in group B. Seventeen per cent of the patients in group A had these conditions.

Bronchopneumonia was found in nearly half of the patients in group B, in which it was more than five times as common as in group A. Atelectasis was uncommon in both groups; however, abnormal bronchial con-

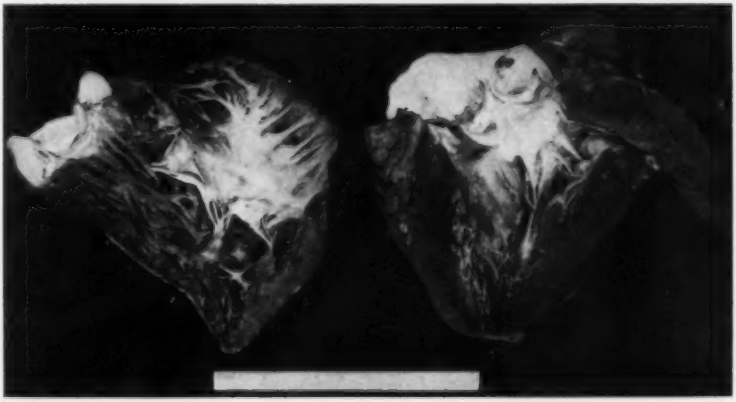

FIGURE 4: Heart showing grade 3 right ventricular hypertrophy with grade 2 dilatation.

TABLE 2—CAUSES OF DEATH UNRELATED TO ASTHMA AMONG 238 ASTHMATIC PATIENTS (GROUP C)

Cause of death	Male	Female	Total	Per cent
Cardiovascular disease	64	18	82	34.4
Malignant disease	47	11	58	24.3
Cerebrovascular disease	10	8	18	7.6
Renal disease	9	6	15	6.3
Postoperative condition	11	4	15	6.3
Periarteritis nodosa	5	4	9	3.8
Trauma	5	0	5	2.1
Suicide	3	2	5	2.1
Cirrhosis	2	1	3	1.3
Other causes	17	11	28	11.8
Total	173	65	238	100.0

tents (mucus, purulent exudate, or both) were found in 97.2 per cent and 71.0 per cent of the cases in groups A and B respectively.

Bronchiectasis occurred in nearly one half of the cases in group B, but in less than 15 per cent of those in group A. Healed tuberculosis was evident in 26 per cent and 39 per cent, respectively, of the cases in groups A and B. These figures do not begin to approach those found by Terplan as representing the incidence of tuberculosis in consecutive necropsy material studied by him during the decade 1930 to 1940. For adult patients, his incidence of positive results was 71 per cent in the age group 18 to 30 years and 90 per cent in the age group 40 to 50.

The incidence of abnormally heavy hearts was 58 per cent and 75 per cent respectively in groups A and B.

Right ventricular hypertrophy (Fig. 4) occurred in 90 per cent of the cases in group B and in nearly 70 per cent of those in group A.

Laryngeal edema and obstruction were noted in three cases of group A (Fig. 5).

Microscopic Findings

Complete obstruction of bronchial lumina by mucous plugs was the most common microscopic lesion in group A, being present in all cases (Fig. 6). It was a less common finding in group B. Extensive numbers

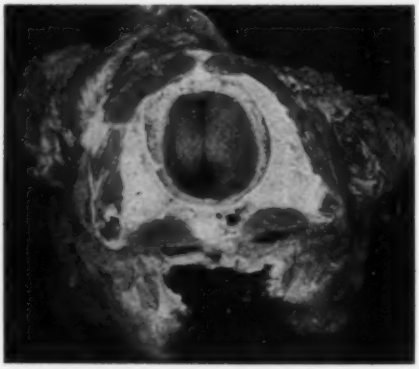

FIGURE 5: Edema of larynx viewed from below. Patient died suddenly during a paroxysm of asthma.

of goblet cells in the bronchial epithelium were also less commonly found in group B than in group A. This finding was usually associated with hyperplasia of bronchial mucous glands.

Hyperplasia of bronchial epithelium was evident in approximately a third of the cases in each group, and frank metaplasia (squamatization) of bronchial epithelium was evident in nearly three fourths of the cases in each group. Figure 7 shows an abrupt change from normal bronchial to metaplastic epithelium, and marked thickening of the basement membrane of the bronchial epithelium. There was a definite relation between the presence of bronchiectasis and the occurrence of metaplasia of the bronchial epithelium, for it was rare to find metaplasia in any case in

Figure 6A

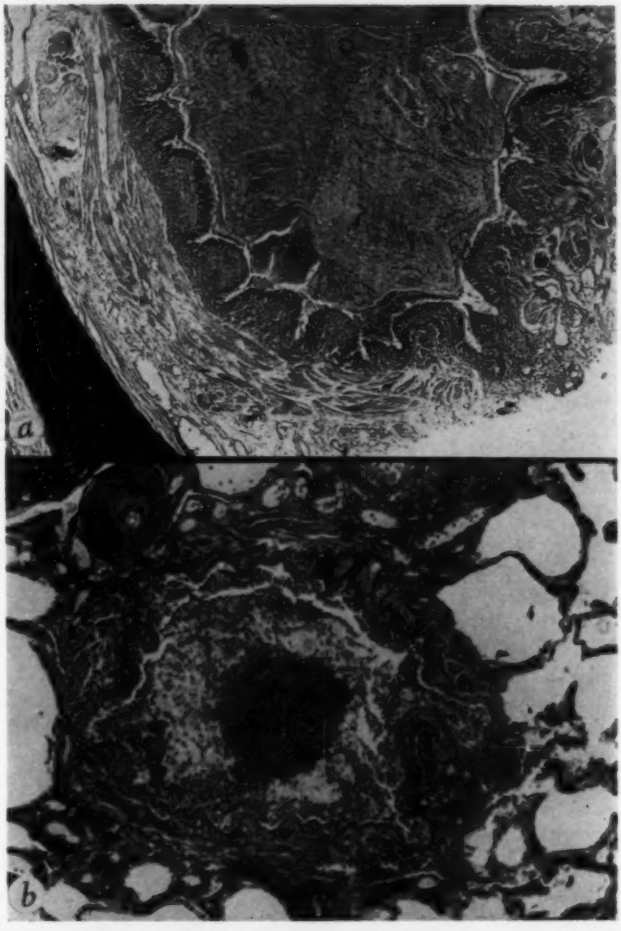

Figure 6B

FIGURE 6A: Bronchus showing complete obstruction by a mucous plug, excessive mucus in the bronchial epithelium, and grade 3 hypertrophy of the bronchial smooth muscle (mucin stain; x30). FIGURE 6B: Smaller bronchus showing complete obstruction by a mucous plug that contains many leukocytes. Also shown are a thick-walled pulmonary capillary, grade 2 hypertrophy of bronchial smooth muscle, and grade 3 thickening of the basement membrane (hematoxylin and eosin; x50).

which there was not also microscopic evidence of severe or moderately severe bronchiectasis.

Hypertrophy of bronchial smooth muscle was common in both groups, although severe hypertrophy was about twice as common in group A (34 per cent) as in group B (16 per cent).

The severity of bronchial smooth-muscle hypertrophy could not be correlated with duration of asthmatic symptoms; however, those pa-

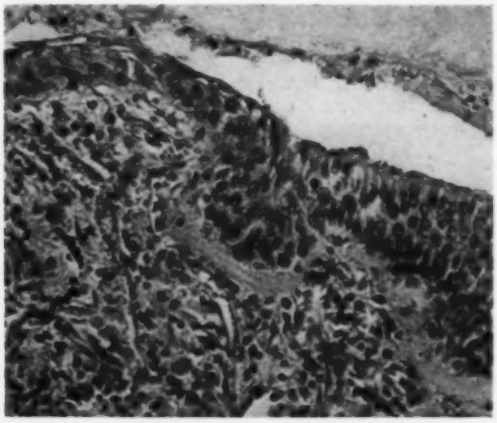

FIGURE 7: Metaplasia (squamatization) of bronchial epithelium with grade 3 thickening of basement membrane (hematoxylin and eosin; x90).

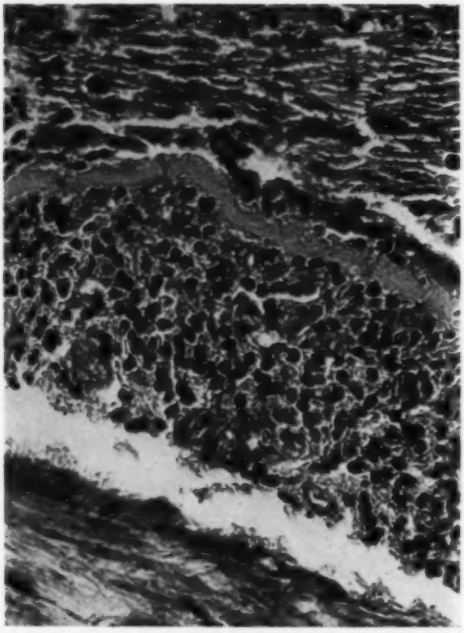

FIGURE 8: Eosinophilic infiltration beneath basement membrane of bronchial epithelium (Dominici stain; x350).

tients with the severest hypertrophy usually also had rather severe thickening of the epithelial basement membrane.

Severe bronchial eosinophilic infiltration (Fig. 8) was much more common in group A than in group B (in 60 and 16 per cent of the cases respectively). No correlation between the severity of bronchial eosinophilic infiltration and duration of asthma was evident.

Bronchial fibrosis was observed in more than 80 per cent of the cases in both groups. Bronchiectasis (Fig. 9) was less common in group A than in group B; in group A more than a third of the patients had no evidence of bronchiectasis, and a little more than half had only minimal bronchiectasis.

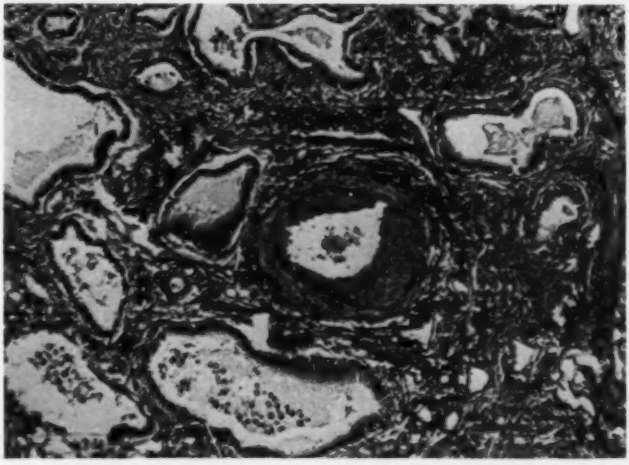

FIGURE 9: Moderately severe bronchiectasis with medial hypertrophy and intimal fibrosis of a pulmonary arteriole (Verhoeff's elastic tissue stain with van Gieson counterstain; x85).

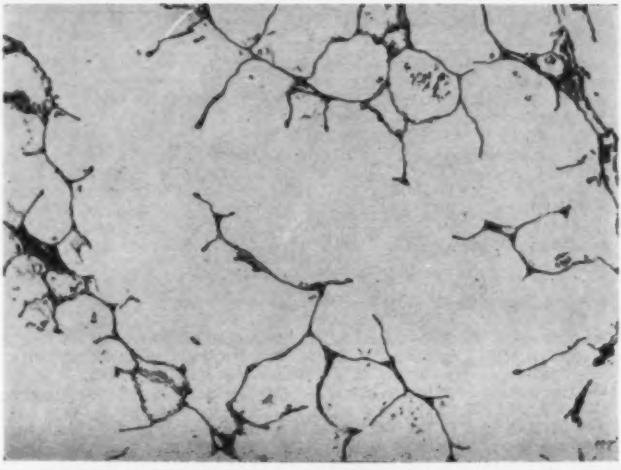

FIGURE 10: Grade 3 emphysema. The clubbed ends on the broken septa represent attempts at healing, and show that the broken septa are not artifacts secondary to preparation of the slide (hematoxylin and eosin; x40).

Microscopic evidence of emphysema was present in essentially all cases (Fig. 10). No correlation between severity of emphysema and duration of asthma was apparent.

Focal atelectasis was common in both groups. Pulmonary arteriolar intimal proliferation was more common in group B, being present in nearly half the cases of that group. Medial hypertrophy was present in more than a third of the cases in both groups.

SUMMARY

One and one half per cent of all patients that come to the Mayo Clinic have bronchial asthma.

Bronchial asthma terminates fatally more often than is generaly thought. In 304 necropsy cases, 17 per cent of the deaths related to asthma occurred within five years after the onset of asthma, and 35 per cent occurred before the age 51.

Of 304 asthmatic patients examined at necropsy, 11.3 per cent died of status asmaticus and 10.4 per cent died of some other asthmatic complication. The remaining 78.3 per cent died of causes unrelated to asthma.

Occlusion of bronchial lumina with thick, tenacious, mucin-staining material is responsible for death in status asmaticus.

The pathologic anatomy of bronchial asthma is that of emphysema, bronchial mucous plugs, bronchial fibrosis, thickening of bronchial base of membrane, and hypertrophy of bronchial smooth muscle.

ACKNOWLEDGEMENT: The authors wish to express their appreciation to Dr. Louis E. Prickman for the initiation of work leading to this report.

RESUMEN

Uno y medio por ciento de los enfermos que vienen a la Clínica Mayo, tienen asma bronquial.

El asma bronquial termina fatalmente más a menudo de lo que se piensa. En 304 necropsias, el 17 por ciento de las muertes relacionadas con el asma, ocurrieron cinco años después del principio del asma y 35 por ciento acontecieron antes de la edad de 51 años.

De 304 asmáticos examinados por autopsia, 11.3 por ciento murieron en status asmaticus y 10.4 por ciento murieron de otra complicación asmática.

Los restantes 78.3 por ciento murieron de causas sin relación con el asma.

Las oclusión de la luz bronquial con material espeso, adherente, que se tiñe como mucina, es responsable de las muertes en status asmaticus.

La anatomía patológica del asma bronquial, es la del enfisema, tapones mucosos, fibrosis bronquial, espesamiento de la membrana basal bronquial y la hipertrofia de los músculos lisos bronquiales.

RESUMÉ

1.5% de la totalité des malades qui viennent à la Mayo Clinique sont atteints d'asthme bronchique.

L'asthme bronchique a une issue fatale plus fréquente qu'on ne le pense. Dans 304 cas ayant pu être autopsiés, 17% des décès repportés à l'asthme survinrent moins de cinq ans après l'apparition de l'asthme et 35% avant l'âge de 51 ans.

Sur les asthmatiques examinés à l'autopsie, 11.3% moururent d'état de mal asthmatique et 10.4% moururent de quelque autre complication due à l'asthme. Les 78.3% restant moururent de causes sans rapport avec l'asthme.

L'obstruction de la lumière bronchique par une matière épaisse, adhérente, se colorant par la mucine, est responsable de la mort dans l'état de mal asthmatique.

L'anatomie pathologique de l'asthme bronchique est la même que celle de l'emphysème: remaniement de la muqueuse bronchique, fibrose bronchique, épaississement de la membrane basale bronchique et hypertrophie des muscles lisses bronchiques.

ZUSAMMENFASSUNG

1½% aller Patienten, die in die Mayo-Klinik eingewiesen wurden, leiden an Bronchialasthma.

Bronchialasthma endet häufiger tödlich als man allgemein annimmt, und von 304 Sektionen ereigneten sich 17% der durch Asthma bedingten Todesfälle innerhalb von 5 Jahren nach Beginn des Asthmas. 35% traten vor dem 51. Lebensjahr ein.

Von 304 asthmatischen Patienten, die autoptisch untersucht worden waren, starben 11.3% im status asthmaticus; 10.4% starben infolge anderer Komplikationen des Asthmas. Die übrigen 78.3% starben aus Gründen, die mit dem Asthma nicht in Zusammenhang standen Verschluß, der Bronchiallumina mit dickem, zähem und sich wie Mucin getarbtes Material ist verantwortlich für den Tod im status asthmaticus.

Die pathologische Anatomie des Bronchialasthmas ist diejenige eines Emphysems, bronchialer Schleimpfropfen, bronchialer Fibrose, Verdickung der Basalmembran der Bronchien und Hypertrophie der glatten Bronchialsmuskulatur.

The Upper Lobe Lesion—Old or New, with Reference to a Case of Aspergillosis (Mycetoma)

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"Routine" or survey chest films uncover two groups of lesion, the "coin" lesion and the upper lobe "scar," wherein the widest range of clinical activity and significance occurs. The importance of investigating and removing solitary circumscribed "coin" lesions is now generally appreciated. However, apical scarring in the form of linear strands, nodular densities, pleural thickenings, unchanging cavitation, etc., are too often disregarded or attributed to healed tuberculosis.

The chaos of fibrotic changes may obscure reactivation of old disease or the development of new disease such as cancer, fungus disease, bronchiectatic sepsis, and so forth. The physician must have a suspicious attitude toward such changes to avoid misdiagnosis. References to a few selected cases, and the appropriate x-ray films, help to illustrate the need for distrust of "healed fibrotic changes" in the lung.

Case 1. C.P.: In 1956, a 39 year-old engineer, as part of an annual physical examination, was found to have an abnormal x-ray film shadow in the right upper lobe. In 1942, 1949, and 1953 chest films had shown an upper lobe shadow. Although noted, investigation of the lesion had never been done, presumably in the latter instances

*Read in part at the Annual Meeting, California Chapter, American College of Surgeons, Palm Springs, January, 1958.
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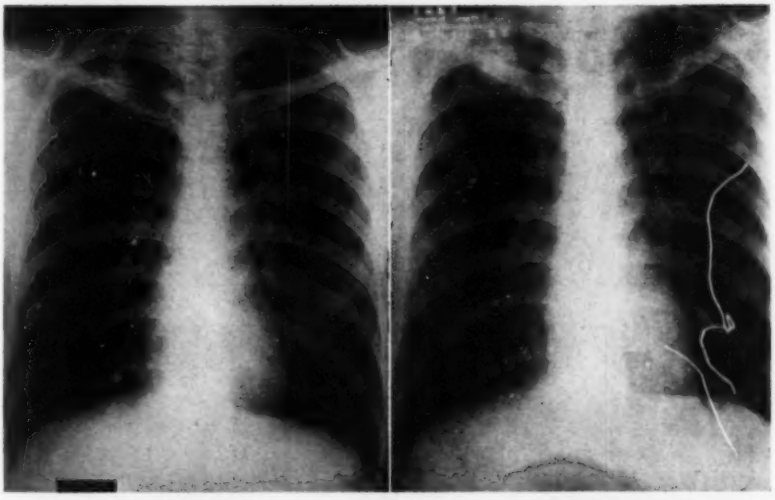

FIGURE 1A FIGURE 1B

FIGURE 1A: *Case 1.* Chest x-ray film April 14, 1953, three years before consultation. There is one large and one small cavitation in the right apex. Pleural thickening is present in both apices, especially on the right.

FIGURE 1B: Chest x-ray film, April, 1956. At the time of surgical consultation: a mycetoma. There is a large thick-walled cavity behind the right clavicle, containing a dense central mass which is separated from the cavity wall by a rim of air. There is diffuse infiltration throughout most of the lobe.

because of its known presence since 1942, at which time it had been thought insignificant. He had had blood-streaking of the sputum off and on since 1945, and a slight, dry, "nervous," cough for several years.

When the 1949, 1953, and 1956 films were obtained and compared directly a marked progression in the extent of the lesion was obvious, and a large apical cavity was now present. This contained a solid mass, separated from the cavity wall by a thin rim of air.* Complete investigation was begun and after three consecutive gastric washings were obtained he was commenced on an antituberculosis regimen because that disease appeared probable. When both culture and guinea pig reports were negative in seven weeks, bronchogenic carcinoma seemed more likely and upper lobectomy was done. The disease was invasive aspergillosis. He is free of this disease 48 months later.

Comment: Depending upon whether or not the Aspergillium infection arose 'de novo' or as a contaminant of an old open tuberculosis cavity, the active infection was missed for either 14 or seven years. Had the lesion been malignant, the patient's fate is obvious. Had it been tuberculosis, involvement of an entire lung or both lungs might have deprived us of one of our leading missile engineers, either due to invalidism or death, and family or working associates might have been infected. Further delay in the diagnosis might have involved spread to other lobes, or to the chest wall. Only by finding the fungus in the sputum could the diagnosis be made preoperatively, and this examination was negative.

Case 2. M.K.: In September, 1957, while hospitalized for a submucous resection, an 18 year-old girl had a chest minifilm, and subsequently a 14 x 17 film, which showed a soft infiltration in the right apex extending down to the first interspace. At the time of emigration from Germany in 1952, five years before, a chest x-ray film had shown a small scar-like density in the extreme apex. A June, 1956 film, four years later, showed definite extension to the lateral first interspace but the responsible physician ignored the finding—possibly because there was no symptom, no cavitation, and a lesion had been noted in 1952.

She was asymptomatic, but had a positive intradermal test for tuberculosis. Special apical views and planigrams of the upper lobe were done without revealing cavitation. Although one physician thought there was further extension in the second interspace between 1956 and 1957, four radiologists felt this was equivocal, and did not believe that the disease could be considered active, on the x-ray film appearance. Nevertheless, guinea pig inoculation of gastric washings was positive for acid-fast bacilli. Marked regression of the infiltrate occurred during the first two months of chemotherapy, thus establishing clinical activity of the tuberculosis.

Comment: The tremendous activity of an 18 year-old girl at school, with the beginning of a career (in this case), and the threshold of family life make this period

*An appearance typical of "mycetoma," or "fungus ball."[1-4]

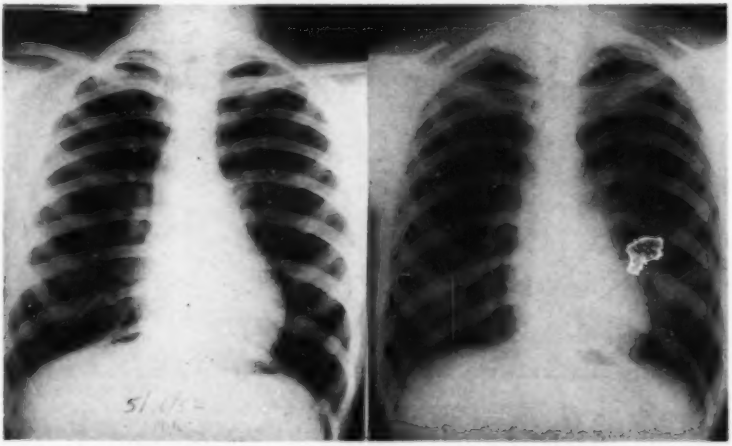

FIGURE 2A FIGURE 2B

FIGURE 2A: *Case 2.* Sixty-four months before diagnosis: There is a small circumscribed apical density. The first interspace is clear.

FIGURE 2B: At the time of diagnosis: There is further extension of the infiltrate to the medial portion of the first interspace.

one of the most dangerous for infection with tuberculosis. The contrast in personal disruption between early treatment of minimal tuberculosis, and that of late treatment of far advanced disease is frightening. There is no substitute for thoroughness in the investigation of the "slight" shadow.

Case 3. O.F.: Because of a severe dry cough, failure to gain weight, and malaise, a 50 year-old alcoholic who was given to much cigarette smoking, had a clinical and x-ray film examination of his chest. Almost hidden behind the right clavicle in the posterioanterior view, but clearly revealed by lordotic and oblique projections, was a 1.8 centimeter hard density with a central lucency. Culture of the gastric washings were negative for acid-fast bacilli but guinea pig inoculation demonstrated the organisms. He could not be persuaded to continue under recommended treatment and failed in his promise to at least return for chest x-ray films every month. One year later, because of hemoptysis, he was examined, and x-ray films then revealed a 4 centimeter in diameter double cavitation at the site of previous pathology. The sputum was again positive for tubercle bacilli. He is now under treatment.

Comment: The initial lesion was dense enough to be a malignancy in spite of the positive guinea pig inoculation. As a tuberculous lesion, it probably represents a small "residual" lesion which finally became active. The noncompliance of the patient affords an opportunity to see the clinical potential of an apparently insignificant "upper lobe shadow."

Case 4. H.B.: A routine hospital minifilm of the chest in this 36 year-old woman showed a shadow casting lesion in the right mid-lung field. Apparently asymptomatic interrogation revealed a transient respiratory infection four months before which had left a slight wheeze, noted occasionally, when lying supine. This could be heard on physical examination. A minifilm taken two years before showed essentially the same lesion. There was some contraction of the upper lobe volume between the two films. When no benefit ensued with four weeks of antibiotic therapy thoracotomy was done; and pneumonectomy for adenocarcinoma. All lymph nodes were normal. The prospect for actual cure is high.

Comment: The internist, who quickly referred this patient when neither a positive bland diagnosis nor a clinical resolution was obtained, commented that had he known about the similar x-ray film appearance two years before, he probably would have assumed the process to be benign, and not asked for surgical consultation. Some bronchogenic carcinomas remain localized for years. It is difficult to decide what interval of no apparent change in size, safely indicates benignancy. Certainly two years is insufficient. Direct comparison of the films themselves are by all means superior to an attempt to correlate written descriptions or interpretations.

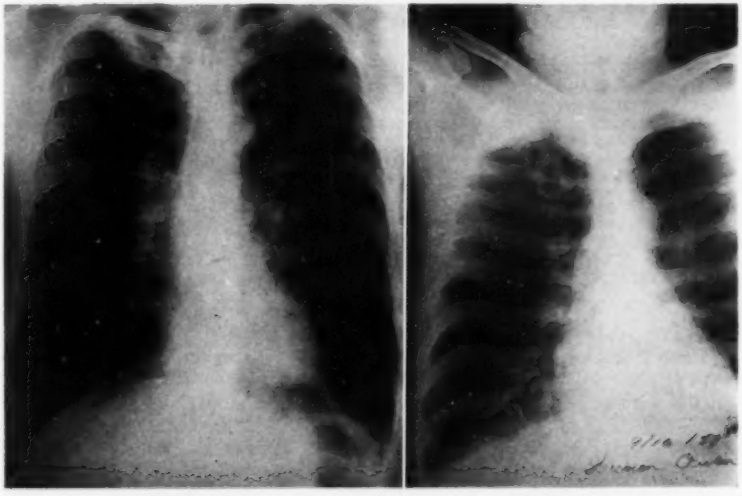

FIGURE 3A FIGURE 3B

FIGURE 3A: *Case 3.* When first seen: there is an ill-defined shadow behind the clavicle and first rib, on the right.

FIGURE 3B: Sixteen months later, with no therapy and considerable personal neglect: a double-barreled cavity, much larger, now replaces the initial small lesion. Fortunately the other lobes remain clear.

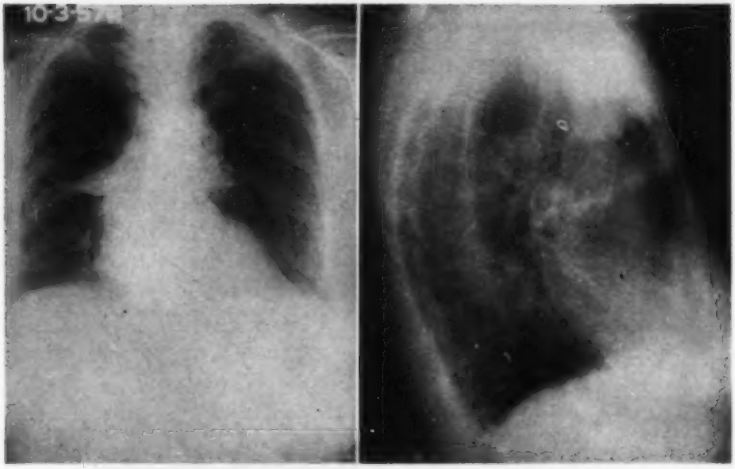

FIGURE 4A FIGURE 4B

FIGURE 4A: *Case 4.* PA projection showing a right hilar mass.

FIGURE 4B: Lateral view: the infiltration extends forward from the hilum, along the course of the anterior segment of the upper lobe.

Discussion

Similar instances, featured either by upper lobe "scarring" or x-ray film examination, and/or a history of prolonged or repeated pulmonary symptoms, where actinomycosis, blastomycosis, coccidioidomycosis, chronic abscess, bronchiectasis, bronchogenic cysts, and so forth, are not rare. Neither upper lobe "scars" of years' duration (cases 1, 2, 4), very small size (case 3), women (carcinoma case 4), age under 40 years (carcinoma case 4), lack of complaints (cases 1, 2, 4), lack of x-ray film evidence of activity (tuberculosis, case 2), nor any simple criterion can be relied upon as an index of inactive scarring. Careful comparison of all available x-ray films, bacteriological study of sputum and gastric washings, intradermal testing, serological titers, therapeutic trial with antibiotics, and pulmonary resection are frequently indicated.

It is probably safe to deem upper lobe shadows inactive if they have the x-ray film characteristics of age, are without question unchanged in appearance and extent over a period of several years, are unaccompanied by clinical illness, and if sputum and gastric washing examinations are negative on both culture and guinea pig inoculation. All other shadows must be viewed with suspicion, carefully investigated, and following closely or explored surgically.

The solitary circumscribed pulmonary density or "coin" lesion has for some years received the serious recognition it deserves and which it formerly did not have. The disregard of upper lobe densities because of the common association with inactive tuberculosis is an equally serious problem and more difficult of resolution. Whereas the principal threat of a "coin" lesion is that of malignancy, the upper lobe density also includes all of the inflammations which may affect the lung tissue.

SUMMARY

1. Fibrotic x-ray densities in the pulmonary apex are so often due to tuberculosis that the presence of the former is almost automatically assumed to indicate the latter.

2. In the absence of clinical symptoms, the second assumption of lesion inactivity is also common.

3. The frequency of such upper lobe "scars" assumes numerical significance if diagnostic errors result from such uncritical evaluation.

RESUMEN

1. La fibrosis observada a los rayos X en los vértices es tan frecuentemente debida a tuberculosis, que casi automáticamente se la señala como indicación de tuberculosis.

2. A falta de síntomas clínicos se supone que hay lesión inactiva comunmente.

3. La frecuencia de tales "cicatrices" en el lóbulo superior, representa errores de significación numérica por tales estimaciones sin base crítica.

RESUMÉ

1. Les opacités radiologiques fibreuses du sommet du poumon sont si souvent imputables à la tuberculose que la présence d'anciennes opacités sert presque automatiquement à l'identification des plus récentes.

2. En l'absence de symptômes cliniques, la notion secondaire le lésion inactive est également banale.

3. La fréquence de telles cicatrices du lobe supérieur semble avoir une signification numérique si des erreurs de diagnostic surviennent après une telle estimation dépourvue de fondement scientifique.

ZUSAMMENFASSUNG

1. Fibrotischen Verdichtungen im Röntgenbild der Lungenspitzen liegt so oft eine Tuberkulose zugrunde, daß das Vorhandensein der ersteren fast automatisch als Indikator für letztere angesehen wird.

2. Im Falle, klinische Symptome fehlen, erfolgt ebenso oft die zweite Annahme, nämlich, daß es sich dabei um inaktive Affektionen handelt.

3. Die Häufigkeit solcher Oberlappen "—Narben"—gewinnt zahlenmässige Bedeutung, wenn sich diagnostische Irrtümer aus einer solchen unkritischen Bewertung ergeben.

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Intrathoracic Manifestations of Malignant Lymphomatous Disease*, **

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Involvement of intrathoracic structures by malignant lymphomatous disease has long been recognized and variations in distribution of lesions described.[1,2,3] Despite this background the possibility of malignant lymphoma is often overlooked in the differential diagnosis of pulmonary and mediastinal disease. In an effort to further delineate the clinical pattern of this condition we have reviewed the problem directing particular attention to pulmonary symptoms and signs and to chest films.

Material

One hundred cases with the diagnosis of malignant lymphoma confirmed by biopsy or autopsy during the period 1950 through 1958 were selected at random from the files of the North Carolina Baptist Hospital. Autopsy material was available in 16 instances. Five diagnostic categories, modified from Custer's classification,[4] were considered to comprise the malignant lymphoma group: Hodgkin's disease, lymphosarcoma, reticulum-cell sarcoma, giant follicular lymphoma and chronic lymphocytic leukemia. Further subdivision within these groups has not been helpful clinically and has afforded no better understanding of the process. Of the patients studied 35 had Hodgkin's disease, 20 had lymphosarcoma, 26 had chronic lymphocytic leukemia, 12 had reticulum-cell sarcoma and seven giant follicular lymphoma. Of these patients 40 have died and 29 have been lost to follow-up. The average duration of follow-up for the entire series was 22 months. Sex distribution is given in Table 1. Of the entire series, 55 were men, 45 women.

Symptoms and Signs

Pulmonary symptoms (Table 2) were infrequent despite a high incidence of intrathoracic involvement as indicated by chest films. Nonproductive cough and dyspnea were the most common symptoms but were rarely troublesome in the absence of infection or pleural effusion. Other symptoms encountered were chest pain, usually a non-specific aching, choking, and hoarseness. Pierce et al[5] have also noted the infrequency of symptoms referable to intrathoracic lesions despite radiologic evidence of extensive disease.

In the absence of pleural effusion, objective evidence of intrathoracic disease on physical examination was unusual. Two patients who had lymphocytic leukemia with widespread pulmonary dissemination had clubbing of the fingers and toes; one of them was also cyanotic as was another with lymphosarcoma. Distention of the jugular and sublingual

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veins, prominent thoracic venous collateral pattern and edema of the upper extremities suggested superior vena caval obstruction in one with Hodgkin's disease and in another with reticulum-cell sarcoma.

Radiographic Findings

Fifty patients had radiographic findings suggestive of malignant lymphoma on the initial chest film and four others subsequently presented x-ray film evidence of pulmonary disease. The site and nature of the lesions are shown in Table 3. Hilar adenopathy was the most common finding in this series being present in 34 of 54 patients with positive films and was more frequently bilateral than unilateral. Twenty-two of them showed enlargement of the paratracheal nodes as well. Parenchymal lesions were present in 23 and were of four types: solitary nodules in two, scattered nodular densities in seven, pneumonic infiltrative lesions in 10 and diffuse lymphatic dissemination in four. Kerley's lines, indicative of interstitial edema or infiltration,[6] were observed twice while cavitation was seen in one patient. Eighteen gave evidence of pleural involvement with effusion present at sometime in all of them. Six presented radiographic findings suggestive of phrenic nerve paralysis, three of the right and three of the left.

In this series, 71 per cent of patients with Hodgkin's disease had chest lesions in contrast to an incidence of 30 per cent in the study of Kirklin and Hefke.[7] In contrast, Vieta and Craver[3] found 74 per cent of their patients with Hodgkin's disease to have x-ray film changes indicative of the process. Parenchymal lesions were present in 23 per cent of our patients with malignant lymphoma whereas Robbins[8] found an incidence of only 7 per cent in a series of 715 cases. Comparison of such series is of questionable value because of differences in pathological classification, methods of treatment and follow-up data.

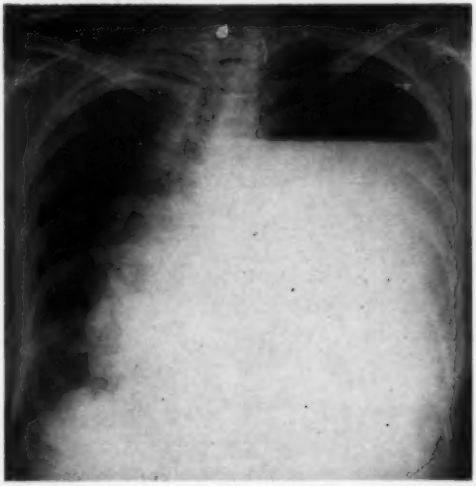

FIGURE 1. Case 1: Massive left pleural effusion in a patient with lymphosarcoma. Note the right apical lesion and the displacement of the mediastinum to the right. The left pneumothorax was produced by previous thoracentesis.

TABLE 1—DISEASE CATEGORIES RELATED TO SEX AND TO THE PRESENCE OR ABSENCE OF ROENTGENOGRAPHIC EVIDENCE OF LYMPHOMA

	Total	Films +		Films 0	
		M	F	M	F
Hodgkin's	35	15	10	7	3
Lymphosarcoma	20	5	5	7	3
Leukemia	26	6	3	10	7
Retic. Cell	12	1	6	3	2
Giant Foll.	7	1	2	0	4
Totals	100	28	26	27	19

Accessory Clinical Findings

Other clinical findings are presented in Table 4. The most frequent physical finding noted was peripheral lymphadenopathy which was present in 73 patients, 39 with positive and 34 negative chest films. Splenomegaly was present in 47 patients, fever in 45, hepatomegaly in 30, anemia in 29, and eosinophilia in 16, 14 with and two without pulmonary manifestations. Anemia was not found in any patient with lymphosarcoma. Abnormal serum proteins (decreased albumin, elevated globulin or both) were found in 24 of 45 while sedimentation rate was elevated in 44 of 60 patients. Intermediate PPD skin test was positive in seven and negative in two individuals. Two with lymphocytic leukemia presented with exfoliative dermatitis.

Examination of pleural fluid in six cases revealed clear yellow fluid in five and colorless in one. Counts were done twice, one showing 2800 white cells and the other 1300 cells/cu. mm. Lymphocytes predominated and no eosinophilia was noted. Cytologic studies of pleural fluid in five instances were not helpful while cultures for acid fast bacilli were negative on two occasions. Chylothorax, a frequently noted complication, was seen once.

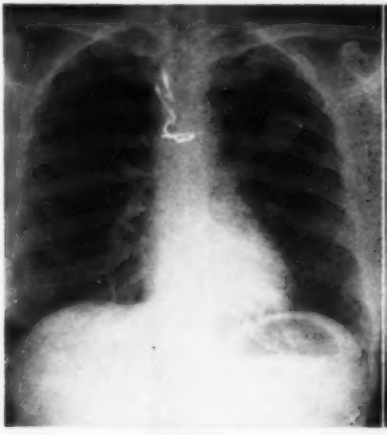

FIGURE 2

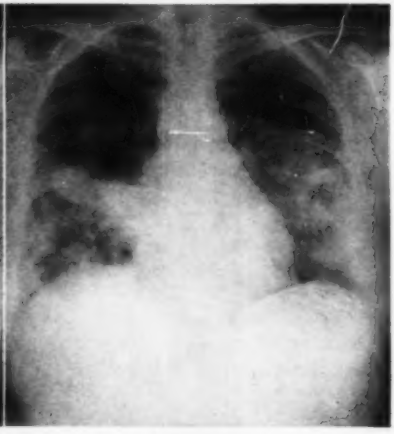

FIGURE 3

FIGURE 2. Case 2: Isolated nodular lymphosarcoma before surgery. FIGURE 3. Case 2: Diffuse recurrence nine months postoperatively.

Differential Diagnosis

Intrathoracic lymphoma may mimic many benign or malignant conditions including tuberculosis, carcinoma, sarcoidosis, "collagen" disease, tularemia, infectious mononucleosis, substernal goitre, dermoid cyst, thymoma and other mediastinal tumors so that tissue diagnosis is mandatory. Conditions with intrathoracic manifestations and peripheral eosinophilia which must be differentiated from lymphoma include: Loeffler's syndrome, coccidioidomycosis, parasitic infestations, polyarteritis nodosa and carcinoma.

The following case reports present some of the problems which arise when only intrathoracic manifestations are present.

Case 1. This 38 year-old white married woman was referred with a six-week history of dyspnea and left pleural effusion. Prior to the onset of her illness, she had been in good health. Physical examination revealed an alert woman with obvious respiratory distress and signs of massive left pleural effusion. The blood pressure was 110/80 and the pulse was 120. Liver and spleen could not be palpated and no peripehral node was felt. Laboratory studies revealed hemoglobin of 16.4 gm. per cent, white blood cells 8,000 and normal differential count. An intermediate PPD skin test was recorded as three plus. During thoracentesis, 1800 cc. of straw colored fluid containing 2800 cells/cu. mm. with 89 per cent lymphocytes and 11 per cent neutrophiles were obtained. Cytological examination of the fluid was not helpful. A right apical infiltrate and massive left pleural effusion were seen on chest film (Fig. 1) and the diagnosis of tuberculosis was strongly considered. She was then transferred to a tuberculosis sanatorium for further study where unusually rapid re-accumulation of pleural fluid led to supraclavicular node biopsy which revealed lymphoblastic lymphosarcoma. She was then returned to this institution where intrapleural and parenteral nitrogen mustard therapy was given without response. Her course was progressively downhill and she expired at home six weeks later.

Comment: This represented a problem in the differential diagnosis of pleural effusion in the presence of a positive intermediate PPD skin test, an apical lesion suggestive of tuberculosis and a normal pleural fluid cytology. The rapid massive re-accumulation of pleural fluid following thoracentesis is more typical of malignancy and this observation led to the correct diagnosis. In retrospect, left scalene fat pad or pleural biopsy might have led to an early diagnosis. The "feel" and thickness of the

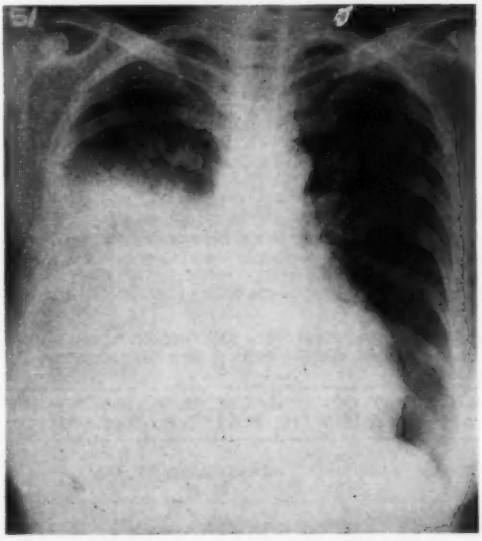

FIGURE 4. Case 4: At autopsy this patient was found to have Hodgkin's disease involving the right lower lobe, right hilar nodes and liver and lipoid pneumonia of the right middle and lower lobes.

TABLE 2—RELATION OF SYMPTOMS TO ROENTGENOGRAPHIC EVIDENCE OF DISEASE

	Chest Film	Hodgkin's	Lympho-sarcoma	Lymphocytic Leukemia	Retic. Cell	Total
Cough	+	7	1	2	1	11
	0	1	1	2	0	4
Dyspnea	+	4	2	2	3	11
	0	0	0	0	0	0
Pain	+	4	1	0	1	6
	0	0	0	0	0	0
Choking	+	1	1	1	0	3
	0	0	0	0	0	0
Hoarseness	+	1	0	0	0	1
	0	0	0	0	0	0
Symptoms	+	12/25	5/10	4/9	4/7	25/54
	0	1/10	1/10	2/17	0/5	4/46

None of the seven patients with giant follicular lymphoma had pulmonary complaints.

pleura observed on inserting the aspirating needle at times suggests extensive infiltration. When these findings are present, a needle biopsy of the pleura is often helpful.

Case 2. A 49 year-old woman was first admitted because of a 3 cm. "coin lesion" in the left upper lobe which had been noted on a routine chest film (Fig. 2). Physical examination was within normal limits while laboratory data included hemoglobin of 13.2 gms. and white blood cells of 8,000 with a normal differential count. Exploratory thoracotomy was done and the pathologic diagnosis of lymphosarcoma made. She did well following a course of postoperative irradiation but a nine-month follow-up chest film showed recurrence of her disease (Fig. 3). At that time she was asymptomatic. A second course of radiation therapy was given with a good response which has been maintained for 21 months.

Comment: The solitary circumscribed pulmonary nodule presents a recurring problem to the physician. Mitchell and Taylor[9] reported an operative series of such cases in which the incidence of malignancy was 39 per cent and pointed out that exploratory thoracotomy is often necessary to establish the correct diagnosis.

Lymphosarcoma, without parenchymal extension or regional adenopathy, was found at surgery; whether this case represents primary lymphosarcoma of the lung[10] is problematical. Resection was thought to have been adequate but extensive recurrence without symptoms was noted nine months later.

Case 3. A 62 year-old white woman was admitted with a history of non-productive cough and progressive dyspnea for one year. For 25 years, she had used oily nose drops excessively. Exploratory thoracotomy elsewhere six months earlier revealed extensive disease in the right lung. Biopsy was reported as lipoid pneumonia and no resection was carried out. Her symptoms persisted and she was admitted to this institution for further evaluation. Physical examination revealed blood pressure of 130/40, temperature 100°F, and pulse 100. Rhonchi and scattered moist and coarse rales were audible throughout both lung fields while dullness and diminished breath sounds were noted at the right lung base. The remainder of the examination was unremarkable. Laboratory data included hemoglobin of 7.4 gms. and white blood cells of 16,300 with a normal differential. Her chest film is shown in Fig. 4.

She was given penicillin and whole blood preparatory to re-exploration of her chest which she declined. She deteriorated rapidly thereafter and expired within two months. Autopsy revealed lipoid pneumonia of the middle and lower lobes of the right lung and Hodgkin's disease involving the lower lobe of the right lung, the hilar nodes and the liver.

Comment: The coincidental occurrence of lipoid pneumonia and Hodgkin's disease was not detected ante-mortem despite exploratory thoracotomy. In this instance, the

TABLE 3—SITES OF INTRATHORACIC INVOLVEMENT IN 54 PATIENTS WITH POSITIVE CHEST FILMS

	Hodgkins (25)	Lympho-sarcoma (10)	Leukemia (9)	Retic. Cell (7)	Giant Foll. (3)	Total (54)
Pleural	7	5	0	5	1	18
Parenchymal	7	5	6	4	1	23
Hilar	15	7	8	2	2	34
Paratracheal	11	3	4	3	0	22

presence of lipoid pneumonia seemed an adequate explanation for her symptoms, although her anemia is difficult to account for on this basis. Unfortunately, a second thoracotomy was declined.

One is tempted to speculate that the use of oily nose drops might have contributed to the development of lymphoma, but there is no clinical or experimental grounds for yielding to such temptation.[11] The pulmonary tissue response to lipoid substances is fibrous and granulomatous and fat is diffusely distributed in most instances.[11] This patient presented an atypical story of lipoid pneumonia, symptoms rarely being this marked. The distribution of lesions suggests that a tumor might have been primary in the chest and that early resection might have been warranted.

Autopsy Material

Thirty-eight patients died during the follow-up period as a result of their disease and two from unrelated conditions, one from carcinoma of the stomach coexistent with Hodgkin's disease of the stomach and the other with myocardial infarction. Autopsy, performed in 16 cases, 13 of whom had positive and three negative chest films, confirmed radiographic impressions in all. Five patients at autopsy, however, were found to have cardiopericardial disease whereas only one was suspected of having these changes during life. No symptom was recorded which suggested such involvement, an experience similar to that of Nabarro[12] who reported physical findings, chest film and electrocardiogram of little help in making an ante-mortem diagnosis. He reported 16 of 60 lymphoma patients to have cardiopericardial involvement at autopsy.

Relation of Intrathoracic Manifestations to the Natural History of the Disease

Analysis of such a series as this is difficult though these data suggest that x-ray film findings of intrathoracic lesions portend greater dissemination of disease. Anemia, fever, and enlargement of the liver and spleen are more common with intrathoracic lesions but the latter are even more frequent than any single one of these findings. There is general agreement that pulmonary involvement indicates widespread disease but feelings are mixed about the prognostic importance of such findings.[2,13,14] Mortality in this series was greater in the group with positive chest films but conclusions cannot be drawn from this because data are insufficient to relate duration of disease to film findings and to the type of disease present.

TABLE 4—ACCESSORY CLINICAL FINDINGS RELATED TO INCIDENCE OF INTRATHORACIC LESIONS

	Chest Film	Anemia <10.5 gms.	Fever	Liver	Spleen	ESR >15	Eosinophilia >5 per cent
Hodgkins	+ (25)	12	18	9	13	16/20	9
	0 (10)	3	5	3	3	5/6	1
Lymphosarcoma	+ (10)	0	4	3	3	2/2	5
	0 (10)	0	0	1	2	3/6	0
Leukemia	+ (9)	4	6	5	8	4/5	0
	0 (17)	3	4	3	13	5/11	0
Retic. Cell	+ (7)	1	4	2	3	3/3	0
	0 (5)	3	2	2	1	4/4	0
Giant Foll.	+ (3)	2	1	2	1	0/1	0
	0 (4)	1	1	0	0	2/2	1
Total		29	45	30	47	44/60	16
	+ (54)	19	33	21	28	25/31	14
	0 (46)	10	12	9	19	19/29	2

Discussion

Several points deserving emphasis emerge from this study. The history and physical examination are of little help in determining the presence or absence of chest disease in lymphoma although the chest film is frequently helpful, particularly when both hilar and paratracheal nodal enlargement is apparent. That intrathoracic findings were present in 54 per cent of our patients and were more frequent than such well recognized features as hepatosplenomegaly, fever, anemia and eosinophilia enhances the value of the routine chest film in diagnostic study. No clinical syndrome or roentgenographic pattern characteristic of any one of the types of malignant lymphoma were encountered.

SUMMARY

In 100 random, pathologically proved cases of malignant lymphoma, 54 presented evidence of intrathoracic disease. Lack of symptoms or signs referable to these lesions was striking.

Hilar adenopathy was the most frequent radiographic finding noted and when associated with paratracheal nodal enlargement was most suggestive of the final diagnosis. Parenchymal and pleural lesions were non-specific in appearance. Eosinophilia when present usually indicated the presence of intrathoracic disease.

Patients who presented positive roentgenographic signs on initial chest studies tended to have more diffusely disseminated disease and seemed to have a slightly worse prognosis than those who presented with normal chest films.

RESUMEN

En 100 casos tomados al azar de linfoma maligno demostrado anatomopatológicamente, 54 tenían evidencias de enfermedad intratorácica. Es sorprendente la falta de síntomas o signos atribuibles a esas lesiones.

La adenopatía hiliar fué el hallazgo mas frecuente y cuando se encontró asociado a crecimiento paratraqueal de ganglios, fué lo mas sugestivo del diagnóstico final. Las lesiones parenquimatosas y pleurales fueron no específicas en apariencia. La eosonofilia cuando se presentó generalmente indicó la presencia de enfermedad intratorácica.

Los enfermos que presentaron signos radiológicos positivos inicialmente tendieron a tener enfermedad mas difundida o diseminada y parecieron tener un pronóstico ligeramente peor que los que tenían radiografía normal de tórax.

RESUMÉ

Dans 100 cas de lymphome malin, choisis au hasard, et prouvés par l'anatomie pathologique, 54 s'accompagnèrent d'une atteinte intrathoracique. L'absence de symptômes ou signes attribuables à ces lésions est frappante.

Une adénopathie hilaire est la constatation radiographique la plus fréquente, et lorsqu'elle est associée à une hypertrophie ganglionnaire paratrachéale, elle est plus évocatrice du diagnostic définitif. Les lésions parenchymateuses et pleurales se présentèrent sans caractère de spécificité. L'eosinophilie, quand on la trouve de façon constante, est en faveur d'une atteinte intrathoracique.

Les malades, chez qui on décèle des signes radiographiques positifs lors des premiers examens thoraciques, ont tendance à être l'objet d'une dissémination et semblent avoir un pronostic légèrement plus mauvais que ceux qui se présentent avec des films thoraciques normaux.

ZUSAMMENFASSUNG

Von 100 unausgewählten, pathologisch-anatomisch bestätigten, Fällen maligner Lymphome boten 54 Anhaltspunkte für eine intrathorakale Erkrankung. Auffallend war das Fehlen von auf solche Befunde sich beziehenden-subjektiver und objektiver Krankheitszeichen.

Hiluslymphknoten-Erkrankungen waren die am häufigsten beobachteten röntgenologischen Befunde und in Verknüpfung mit einer Vergrößerung der paratrachealen Lymphknoten waren sie besonders verdächtig bezüglich der endgültigen Diagnose. Herde im Parenchym und an der Pleura waren dem Augenschein nach nicht spezifisch verdächtig. Lag eine Eosinophilie vor, so zeigte sie gewöhnlich das Bestehen einer intrathorakalen Erkrankung an.

Kranke, bei denen gelegentlichder ersten Thoraxuntersuchung bereits röntgenologische Befunde vorlagen, hatten die Tendenz zu mehr diffus ausgebreiteter Erkrankung und scheinen eine etwas schlechtere Prognose zu haben, als diejenigen, die mit einer normalen Thorax-Röntgenaufnahme zur Vorstellung kamen.

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Hydatid Cyst of the Lung*, **

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Hydatid disease is not as rare in our part of the world as suggested by the paucity of published reports. The tendency of the disease to remain quiescent over long periods and lack of availability of proper diagnostic facilities on a large scale contributed to the lack of knowledge of incidence of the disease in this area.

Surveys to investigate the incidence of hydatid disease in man and animals were carried out at the Medical College, Amritsar. During the five year period 1950-55, incidence of hydatid disease was .009 per cent of 42,948 admissions in the Medical College Hospital, Amritsar. Eight and four-tenths per cent of the 460 dogs revealed Taenia Ecchinococcus granulosus in their intestines. Three and one-half per cent of 1,095 goats and sheep examined in the local slaughter house harboured hydatid cysts.[1]

These, along with some of the other published reports,[2-7] indicate the endemic nature of the disease in India.

During the last five years, ten cases of pulmonary hydatid cysts were treated in our unit.

TABLE 1—AGE AND SEX INCIDENCE

Sex	1 to 10 years	10 to 20 years	20 to 30 years	30 to 40 years	Above 40 years
Male	1	1	2	—	1
Female	—	—	1	4	—

Seven out of 10 patients were between 20-40. The youngest in this series was nine years old and oldest was 56.

Symptomatology

Hydatid cysts of the lung are known to remain silent for a long period without causing any or only minimal symptoms. The symptoms arise either as a result of pressure of the growing cyst on the surrounding structures or most commonly because of the complications which befall the cyst.

Cough with expectoration was the commonest symptom and was present in all. This was the first symptom in six. The character of the sputum varied from mucoid to frankly purulent. This was accompanied by bouts of fever in five. In one, the onset was acute with high fever.

Haemoptysis, the next common symptom, was noted in seven and was the presenting symptom in three. Most often the haemoptyses were small and recurrent, but in one, the illness started with a bout of profuse haemoptysis. Because of the cough with expectoration, accompanied by fever and haemoptysis, two cases were treated as tuberculous for some time in outside clinics. It seems important to keep in mind hydatid dis-

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**Presented at the 5th International Congress on Diseases of the Chest, American College of Chest Physicians, Tokyo, Japan, September, 1958.

ease as one of the causes producing such symptoms, especially in areas where the disease is endemic. Four patients complained of pain in the chest and it was the presenting symptom in two. In one, the pain was localized to the area overlying the cyst and in this case the cyst was infected and adherent to the parietes. In others, the pain was mild, inconstant and vague in nature and in these there were no adhesions or infection.

One of the patients formerly had attacks of paroxysmal dyspnoea and urticaria as manifestations of anaphylactic phenomenon.

Diagnosis

Many pulmonary hydatid cysts are diagnosed on a routine skiagram of the chest and many symptomless cases are likely to be encountered if x-ray film surveys are done in endemic areas. The diagnosis is not always definite on radiological evidence alone and frequently it may only indicate the presence of a radio-opaque mass with a suspicion that it may be a hydatid cyst.

Simple pulmonary hydatid cyst revealed itself by an ovoid or round shadow clearly demarcated from the normal lung (Figure 1). It may be difficult to come to a definite diagnosis. In one of the patients such an appearance suggested the diagnosis of hydatid cyst, but on exploratory thoracotomy, it was found to be a neuro fibrosarcoma arising from the chest wall (Figures 2 and 3).

Complicated cysts produce characteristic radiological appearances depending upon the extent of separation of cyst wall from the pericyst (Figure 4), establishment of communications with the bronchi, degree of

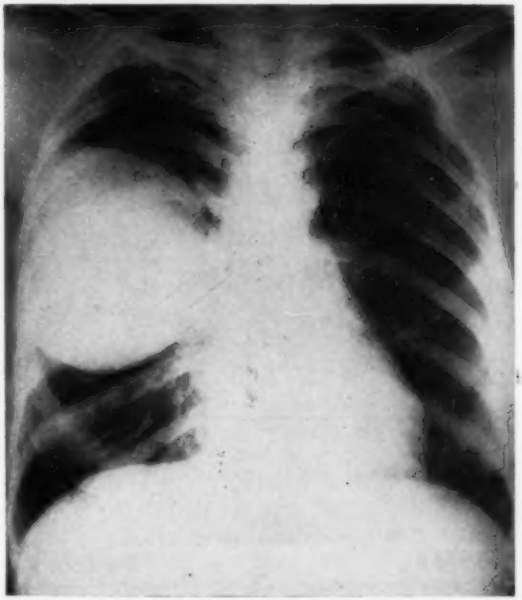

FIGURE 1: Uncomplicated hydatid cyst in a woman aged 28 years.

changes such as atelectasis, infection and bronchiectasis in the adjacent lung parenchyma and calcification of the cyst.

Differentiation of hydatid cysts of the lung from hepatic cysts bulging through the diaphragm may present a problem. Lateral skiagram of the chest and skiagram taken after pneumoperitoneum help to elucidate this point, but at times it may be difficult to do so without resorting to exploratory thoracotomy as was necessary in one of our patients (Figure 5).

Casoni intradermal test was positive in 70 per cent of the cases in which it was done. It was not much relied upon due to the false positives which were noted during this period.

Complement fixation test was done in two cases and it was positive.

Eosinophils were not significantly increased in our cases. Eosinophilia is not of much diagnostic importance specially in areas where other helminthic infestations are common.

Treatment

Treatment of pulmonary hydatid disease is surgical indeed. Expectant treatment or any other medical treatment suggested so far in the literature[5] cannot be relied upon. Such methods must often fail and may leave the patient suffering from pulmonary suppuration in addition to the danger due to anaphylaxis, sudden asphyxia and development of secondary daughter cysts. The aim should be that a pulmonary hydatid cyst must be treated surgically without undue waiting, because a cure can almost always be achieved. Various surgical procedures are available and depending upon the pathological manifestations, presence of infection, secondary changes in the lungs, certainty of diagnosis and the general condition of the patient, most suitable method for an individual patient, can be selected. The different procedures carried out in this small series of patients are shown in Table 2.

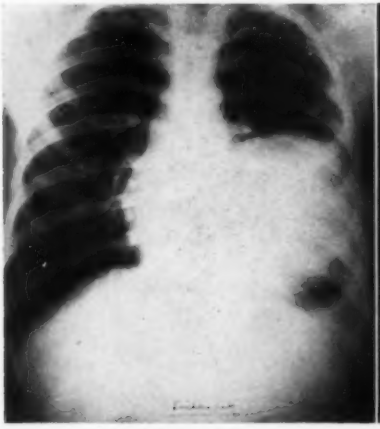

FIGURE 2

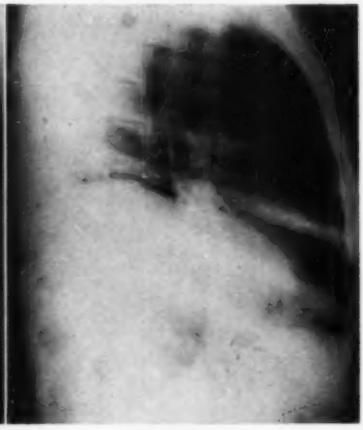

FIGURE 3

FIGURES 2 and 3: Antero-posterior and lateral view of the chest showing neurofibrosarcoma arising from the chest wall.

TABLE 2—TYPES OF OPERATIONS DONE

Type of operation	No. of patients	Indications
1. Enucleation of the cyst (Barret's technique)	2	Simple cyst.
2. Pulmonary Resections:		
Lobectomy	2	Bronchiectasis, infected cyst.
Pneumonectomy	2	Uncertain diagnosis in complicated cysts.
3. Drainage of the cyst:		
Open thoracotomy	2	Complicated cysts.
Rib resection	1	Infected bilateral cysts.
4. Drainage hydatid empyema	1	Empyema with pleural and pulmonary hydatid cysts.

Enucleation of the Parasite Intact

A technique suggested by Barrett[9,10] for the treatment of simple hydatid cysts was successfully applied in two patients. This is a useful procedure as there is no loss of functioning pulmonary tissue and there is less post-operative morbidity as compared to the other methods. The space occupied by the cyst is obliterated by the expansion of the compressed pulmonary tissue in a period varying from a few days to a few months depending upon the amount of fibrous tissue in the pericyst. The often raised objection of accidental rupture of the cyst during expulsion and soiling of the wound with live hydatid material can be successfully met with most often, provided the anaesthetist and the surgeon perform the procedure correctly and the whole area is packed properly before undertaking the procedure. Removal of the pericyst was not attempted in these patients and does not often seem to be necessary.

Pulmonary Resections

Segmental, lobectomy or pneumonectomy have to be undertaken in some patients. Indications for following such a procedure vary according to the choice and experience of the surgeon in various procedures and

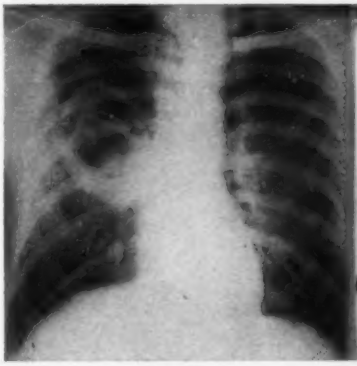

FIGURE 4

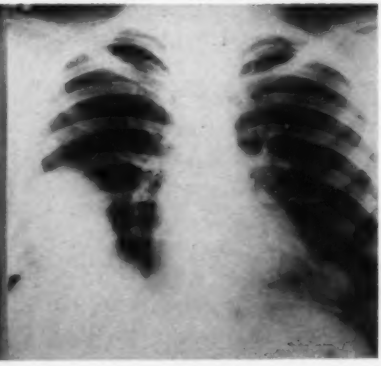

FIGURE 5

FIGURE 4: Complicated hydatid cyst showing wavy appearance by separation of endocyst from pericyst. FIGURE 5: X-ray chest posteroanterior view. Hydatid cyst liver bulging through the diaphragm.

the pathological manifestations encountered. Irreversible changes such as bronchiectasis or suppuration in the surrounding lung demand necessarily such a procedure, rather than simple removal of the cyst. Right lower lobectomy was done in two patients. In one there was associated bronchiectasis and in the second the cyst was infected and deeply situated in the substance of the lobe. Two patients were treated by pneumonectomy because of suspicion of malignancy as resection should always be preferred over enucleation of a tumour of doubtful nature. A definite diagnosis could not be made prior to section of the removed lung. It is felt that in such a situation which can often arise, if possible, lobectomy should first be done, specimen examined and pneumonectomy be done if the lesion so demands. Such a procedure, if followed, helps in preserving normal pulmonary tissue. But in both of our patients lobectomy was not technically possible without interferring with the diseased area because of the marked inter lobar adhesions and extensive inflammatory changes in the surrounding lung parenchyma. Marked haemorrhage or suppuration of the cavity left after removal of the parasite is stated to require pulmonary resection (Susman)[11-13] but such a problem was not encountered in any of these cases.

Drainage of the Cyst

Three infected cysts were treated successfully by this procedure. In two open thoracotomy was done but during the operation condition of the patients deteriorated so the chest was closed and drainage of the cysts was done a few days later, after the adhesions had formed with the parietes.

The third patient, a nine year-old child who had bilateral infected hydatid cysts, was in poor general condition due to prolonged cough, expectoration and fever, not fit for any other surgical procedure, was treated by a two stage drainage operation on the left side under general endotracheal anaesthesia. During the second stage procedure a lot of hydatid material and pus was aspirated through the endotracheal tube when it supposedly was being expelled out of the side of operative intervention, but to our surprise, postoperative skiagram revealed disappear-

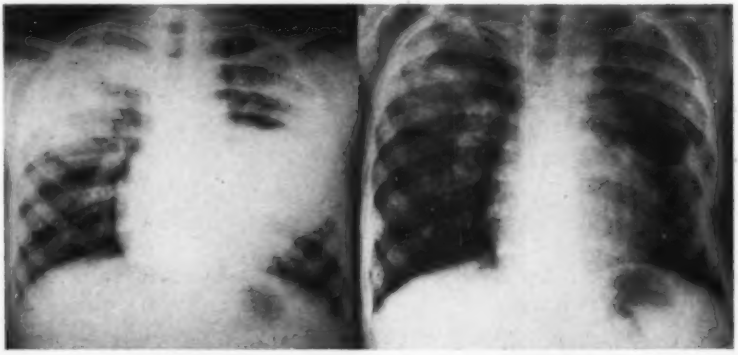

FIGURE 6 FIGURE 7

rance of the hydatid cyst from the contralateral side also and in a few days the lung completely expanded (Figures 6 and 7). Two stage drainage operation, though considered obsolete because of uncertainty of adhesion formation, prolonged post-operative morbidity due to prolonged drainage and availability of better procedures, may still be required in a desperate patient unsuitable for any other procedure.

Hydatid Empyema

It should be drained at the first instance, followed by removal of the hydatid cyst from the pleura and the lung, but if there are irreversible changes in the lung, such a condition should better be treated by pleuro-pneumonectomy. One such case is included in this report where drainage of the empyema and removal of some of the cysts from the pleura was done but there was extensive involvement of the pleura and the lung. Pleuro-pneumonectomy could not be done because of poor general condition of the patient. Sinus is still persisting.

SUMMARY

This report, based on ten cases of hydatid cysts of the lungs, shows that cough and expectoration with or without fever were most often accompanied by small, recurrent haemoptysis. Anaphylactic manifestations were present in one patient.

Pulmonary resection was performed in four cases, enucleation of the cyst in two and drainage in four cases.

Two-stage drainage operation, considered obsolete, may still be required in desperately ill patients unsuitable for any other procedure as in one of these cases.

RESUMEN

Esta communicación que se basa en 10 casos de quistes hidatídicos pulmonares, muestra que la tos y la expectoración con o sin fiebre fué acompañada lo más a menudo de hemoptisis pequeñas, recurrentes.

Las manifestaciones anafilácticas se encontraron en un enfermo. Se hizo resección pulmonar en cuatro, enucleación del quiste en dos y canalización en cuatro.

La operación de canalización en dos tiempos, considerada anticuada, puede aún requerirse en los enfermos muy gravemente afectados que no son adecuados para otro procedimiento, como ocurrió en uno de estos casos.

RESUMÉ

Cette publication, basée sur 10 cas de kystes hydatiques des poumons, montre que la toux et l'expectoration avec ou sans fièvre sont le plus souvent accompagnées de petites hèmoptysies récidivantes. Des manifestations anaphylactiques existaient chez un malade.

Une résection pulmonaire fut pratiquée chez chaque malade, l'énucléation du kyste chez deux d'entre eux, et un drainage dans quatre cas.

Une intervention de drainage en deux temps, considérée comme surannée, peut encore être nécessitée chez des malades dont l'état semble désespéré, et qui ne sont pas justiciables d'un autre procédé, comme ce fut le cas pour l'une des observations rapportées.

ZUSAMMENFASSUNG

Dieser Bericht, der von 10 Fällen einer hydatiden Lungenkrankheit ausgeht, zeigt, daß Husten und Auswurf mit oder ohne Fieber besonders häufig von kleinen, sich wiederholenden Haemoptysen begleitet waren. Anaphylaktische Manifestationen kamen bei einem Kranken vor.

In 4 Fällen wurde eine Lungenresektion vorgenommen, bei 2 Fällen eine Enukleation der Cyste und viermal eine Drainage.

Die zweiseitige Drainageoperation, die nicht mehr gebräuchlich ist, kann noch erforderlich werden für besonders schwere Fälle, für die jede andere Maßnahme, wie sie für die vorausgegangenen Fälle beschrieben worden sind, nicht mehr in Frage kommen.

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SECTION ON CARDIOVASCULAR DISEASES

Surgical Anatomy of the Coronary Arteries

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Investigations of the last decade have led to a considerable change of certain concepts regarding coronary heart disease. This change has come in waves from many directions but particularly from the surgical laboratories. In the quest for new frontiers in the exciting developments of cardiac surgery during this period, contributions in physiology and pathology have been keeping pace with surgical techniques, and now it has even become possible to review critically and with great reward, the basic anatomy of the coronary arteries; both in the normal state, and in the anatomical changes associated with arteriosclerosis of these vessels.

When the standard anatomy and atlases with which we are so familiar were prepared, it was in a time when the average length of life was in the neighborhood of 45 years. The degree and widespread incidence of atherosclerosis which is prevalent today was then less marked, and to the pathology laboratories, came in large numbers the tissues of younger individuals dying of such diseases as pneumonia, tuberculosis and even syphilis. It is understandable that under such circumstances the clarity of the picture of atherosclerosis could not approach that of today.

In order to resolve the confusion that was caused by seeing different pictures at operation than was expected by prior knowledge of anatomy obtained from standard sources, a critical study of Schlesinger preparations and 200 fresh hearts obtained at autopsy, was undertaken to see what could be learned about the anatomy of the coronary arteries in all types of hearts.

Six hundred x-ray plates of Schlesinger injected hearts, prepared in accordance with Schlesinger's original method, were made available for study. The majority were excellent preparations, showing both arteries clearly. Many, however, demonstrated only one of the two sides filled, and there were many in which the injection was felt to be inadequate for our purposes. Three hundred were selected as being well enough prepared to be meaningful, and these were carefully studied for several features which they could exhibit as follows:

(1) Relative frequency of left and right coronary preponderance, and its relation to atherosclerosis.

(2) Number and diameter of the branches of the two main vessels.

(3) The presence of, and types of, intercoronary anastomosis.

(4) Special features that might have a bearing upon surgical approach to the problem of atherosclerosis.

Presented in part as an exhibit at the American Medical Association Convention, San Francisco, June, 1958, and at the American Heart Association Convention, San Francisco, 1958.

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In complete accord with Schlesinger's observations, it was found that no two human hearts were alike regarding the picture of their coronary tree, and that each one was an individual unto itself. In general, the findings were identical with those of Schlesinger and Zoll in that it was found that the right coronary artery is far and away, in the largest proportion of cases, the larger artery of the heart, and must be given greater consideration in our thinking regarding coronary occlusion. It was found that the coronary arteries may be delicate and numerous in number, or may be sturdy and infrequent in their initial branching; one may compare the two types with the branching of a Mariposa pine and a Douglas fir, and that in between these two extremes there are many degrees of intermediates. It is worth while to mention that seldom did a heart exhibit both types of branching in the same specimen. Rather, the type of branching was consistent for any heart in both coronaries. As one will see in the foregoing material, the amount of blood supply to any one portion of the heart was a remarkably constant feature, no matter from which artery it happened to arise. A system of nomenclature of the coronary vessels was devised for the purpose of classifying thm as to number and location.

In general, the arteries were of a fairly comparative mean caliber. The term MICROARTERIOSIS CORONARIAE for the hearts in which main arteries and branches were of small caliber and branched finely, and the term MACROARTERIOSIS for the reverse was adopted.

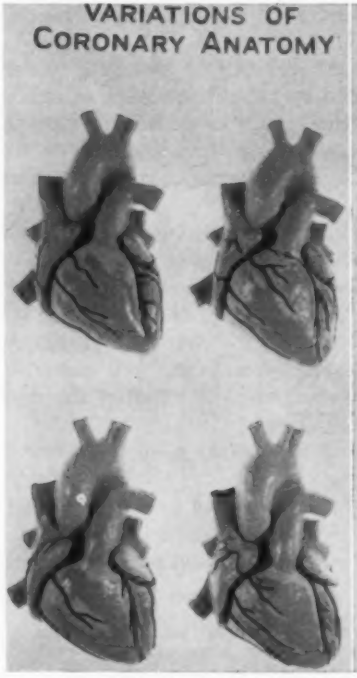


FIGURE 1

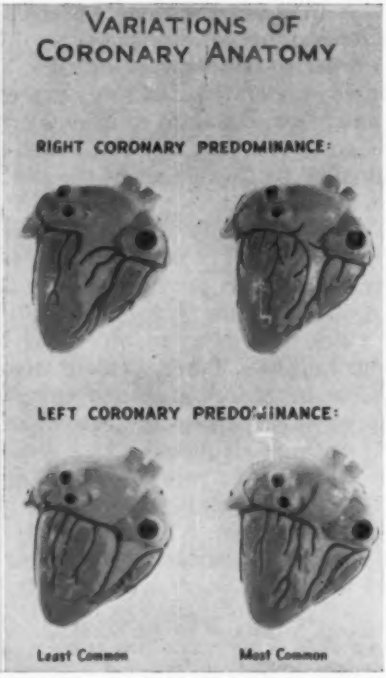


FIGURE 2

Embryology

Embryology texts demonstrate the coronary arteries early in the life of the embryo as small vessels arising from the right and left side of the truncus arteriosis and branching both anteriorly and posteriorly. In the formation of the aorta and the pulmonary artery, rotation and asymmetrical growth of the vessel walls must account for the positioning of the coronary arteries in the adult heart.

Coronary Orifices

1. Location as to Valve Leaflets

The actual location of the coronary orifice, within the aorta itself, is variously described in anatomical atlases and standard text books. Some have the coronary orifice arise in the sinuses of Valsalva, behind the valve leaflet and some, both the orifices from the anterior portion of the aorta. In all of the hearts studied, the coronary orifices arose above the line of reflection of the aortic valves. It is obvious that should this not be the case, it would constitute a physiological handicap, as upon opening the aortic valve, the occlusion produced by the valve leaflets against the coronary vessels would preclude flow during the systolic phase to the coronary orifices. Happily, this was not found to be so and the findings agree with those who place the orifices above the line of reflection of the valve. Actually, there was a considerable amount of variation in the height above the valve leaflet, some coming off as high as a centimeter above the line of reflection.

2. The Location of the Take-Off of the Coronary Arteries as Regards the Anterior Posterior Axis.

A considerable variation of the origin of the ateries was noted. Gray's Anatomy was found somewhat confusing in that the text describes that the left coronary artery arises from the left posterior aspect of the aorta, but on the same page demonstrates in their color plate the origin of the left coronary from the anterior aspect of the aorta. The investigations indicated that in 93 per cent of the hearts their text is correct;

TABLE 1—CODING OF CORONARY VARIATIONS
Study of 200 hearts at autopsy and 300 Schlesinger-injected hearts

Right Coronary Predominance		55 percent
Branches to:		
Right Ventricle	4.8	
Septum	3.2	2.4 from Rt. Coronary, 6.2 from Left
Left Ventricle	8.6	
Right Atrium	2.5	
Left Atrium	2.8	
Balance		9 per cent
Branches to:		
Right Ventricle	4.8	
Septum	3.5	
Left Ventricle	8.2	
Right Atrium	2.2	
Left Atrium	2.5	
Left Coronary Predominance		36 per cent
Branches to:		
Right Ventricle	4.5	
Septum	3.2	
Left Ventricle	8.0	
Right Atrium	2.0	
Left Atrium	2.6	

the standard take-off of the left coronary is in the left posterior aspect of the aorta, at approximately 65 degrees from the posterior axis. Variations in location, however, are not rare and perhaps 15 degrees is a standard deviation. A few arteries were found to extnd as far forward as 65 degrees from the anterior axis and all variations between the two points mentioned were noted.

The right coronary artery arose almost always from the right anterior surface of the aorta. Similarly, some degree of variation was noted and a normal standard deviation of approximately 20 degrees was observable in the number studied. The center point of the angle of take-off was approximately 35 degrees from the anterior axis.

The nature of the orifices was interesting as observed from the interior of the aorta. The size of the orifice corresponded to the predominance of the artery which will be discussed later. In many cases, two or three orifices could be seen within the orifice of the right coronary, much as one sees the orifices of the upepr lobe bronchus during bronchoscopy, a large intermediate branch going to the right atrium in practically every case, a second branch traversing posteriorly and a third anteriorly and in the atrial ventricular groove.

The left coronary ostium, however, was more often observed to be single although in approximately 25 per cent of the hearts a double orifice was noted, the small vessel in this case being the left atrial artery. The bifurcation of the left common coronary occurred on an average of one centimeter and a half from its origin, the course of the main stem artery being almost tangent to the aorta coming to the junction of the atrioventricular groove and the left border of the pulmonary artery

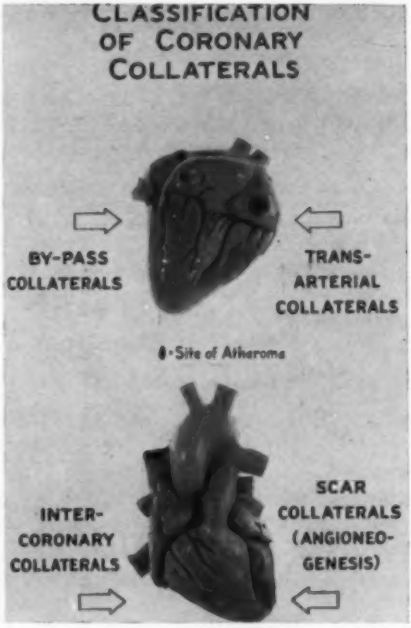


FIGURE 3

where it divided into the interventricular artery and the atrio-ventricular vessl (or in other terminology, the anterior descending coronary and the circumflex branch.)

The Atrial Arteries

The greatest surprise of the study was the distribution and the importance of the atrial arteries, not only as anatomical constancies but more interestingly, their role as a source of collateral circulation for the atrioventricular vessels. The atrial arteries averaged 3.5 in number to either side. Almost constantly there was an artery, which on the right side was derived from the first half centimeter of the coronary orifice itself, and on the left, from the first centimeter distal to the orifice. This vessel immediately coursed upward and distributed itself over the atrium; the first artery constituting in approximately 60 per cent of the instances, the largest artery of the atrium. The remainder of the atrial arteries originated in the atrioventricular groove from either the right or left atrioventricular arteries (right coronary or left circumflex) and coursed upward, distributing branches over the atria. The Schlesinger injections revealed a suprising number of interarterial and transarterial anastomosis in the atrial vessels, providing a ready-made collateral circulation whenever atheromas were present in the atrioventricular vessels. It was frequently apparent that segmental occlusions of the atrioventricular vessels occurred but did not disrupt the distribution of blood throughout the areas supplied by these vessels because the skip areas were furnished with a by-pass by route of the atrial vessels. As the atrioventricular vessels are in general the hinterland of atheroma formation, the role of the atrial vessels as collaterals cannot be overemphasized.

That considerable pressure differentials in various parts of the coronary tree exist was attested by the presence of tortuous collateral vessels

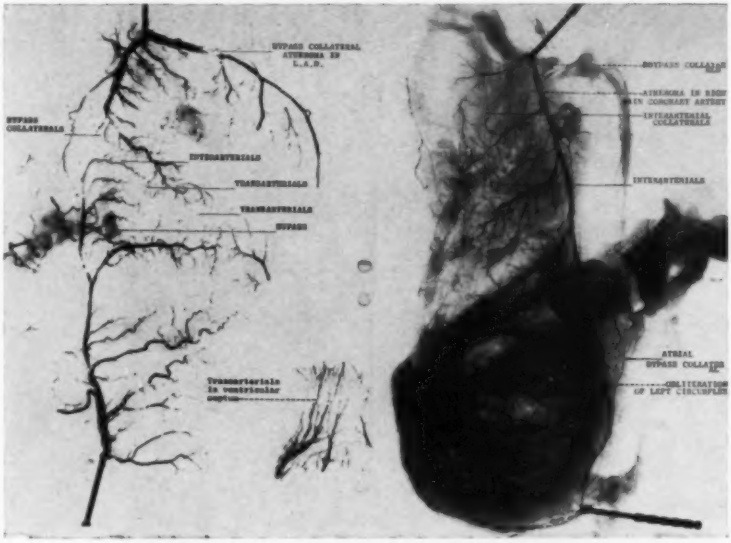


FIGURE 4

FIGURE 5

forming transarterial and interarterial collaterals and sometimes extending for great lengths along the walls of the atria.

Ventricular Arteries

For the sake of descriptive nomenclature and the proper concept of the distribution of blood from the arteries of the ventricles, the terms of right coronary, left anterior descending and left circumflex should give way to more descriptive names of "left atrioventricular artery," "left interventricular artery" and "right atrioventricular artery." These name suggest and describe the location of the vessel and the distribution of the blood from it. It was interesting to note that the anterior interventricular artery (anterior descending) gave, in most cases, very few branches to the right ventricle. Dissection of the interventricular groove, demonstrated however, that the right branches of the vessel continued around the myocardium of the left ventricle in the septum and for the most part supplied the septal portion of the left ventricle. One notable exception, however, was an almost constant artery, Vieussen's Ring, along the apex of the right ventricle which supplied the outflow tract of the right ventricle and coursed behind the pulmonary artery. This vessel has been described in detail by James and Burch[1] and the reader is referred to their excellent article for a complete elaboration of the functional importance of this vessel.

The same authors[2] have pointed out the almost constant presence of the first branch of the right coronary artery ascending along the right atrium to the superior vena cava. The ramus ostii cavae superioris artery which in their series of 53 hearts was demonstrated in 49. We also found this vessel to be present in the greater proportion of cases, although the exception proved the rule and in many cases this area was supplied by the second or even the third atrial branch of the right

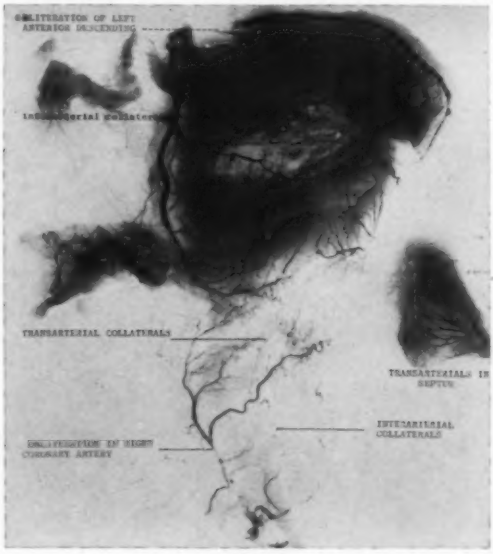


FIGURE 6

coronary. As James and Burch described, the right coronary artery quite commonly made a U-turn posteriorly, giving branches to the septum at this point and especially in that greater proportion of cases where branches of the right coronary passed the posterior interventricular groove and gave branches to the left ventricle.

The average number of arteries, penetrating the septum from the descending was counted and found to be 3.2, these constituting the larger arteries of the septum in the greater proportion of cases. The arteries from the left anterior descending were found to supply approximately ⅔ to ¾ of the septum, being much longer than the arteries from the posterior interventricular artery which will be described later. Although sclerosis both of the segmental and continuous type were prominent in the surface vessels of the left anterior descending artery, the septal vessels rarely exhibited advanced arteriosclerotic changes.

The left coronary artery was found to be the dominant artery in only 23 per cent of the hearts studied. This is slightly lower than Schlesinger's original figures. The left interventricular artery gave an average of 3.1 branches to the left ventricle and only in 7 per cent of the cases gave off the posterior interventricular artery, where it gave branches to the septum. It is interesting to note that in the Stereoscopic Atlas,[2] the study of the injection heart in three-dimensional roentgenography showed the coronary circulation to the left ventricle coming almost entirely from the left coronary artery. It is an unfortunate circumstance that the heart seelcted for this work was so left-coronary predominant that this beauiful demonstration might lead to the erroneous conclusion on the part of those who studied this atlas, that this represented the standard situation, for it is the rare excepion and in our studies, 93 per cent of the time did not exist. The left coronary terminated, as a rule, making an oblique descent toward the posterior interventricular groove, there being in the back of the heart, between the two vntricles and th atriovntricular groove, a relatively amuscular triangle; also avascular in nature, which

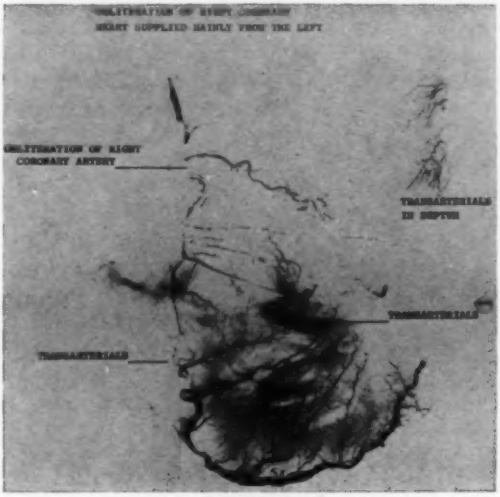
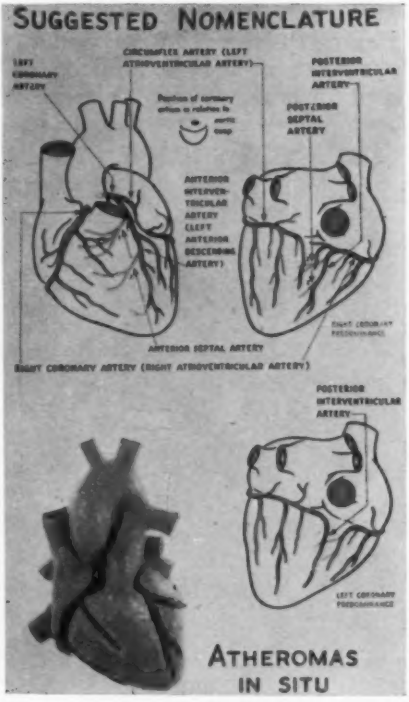


FIGURE 7

was observesd to be an anatomical no-man's land of coronary circulation. Although Gray's anatomy and Cunningham and several of the English anatomy texts show a linear communication between the left and right coronaries, along the interventricular groove posteriorly, this was not observed in a single instance in the series of hearts studied and due to the triangular no-man's land in this region, it was concluded that this was either an extremely rare anomaly or a figment of the artist's imagination, not corrected by the anatomist.

The Right Coronary Artery

The right coronary artery arises, as described previously, from the right anterior aspect of the aorta, overhung by the right auricular appendage and visible when this structure is pulled upwards. The first branch of the right coronary is almost always the right atrial artery, there being an average of 3.5 arteries given to the right atrium along its course. Depending upon the origin of the artery, it descends downward and to the right to the atrioventricular groove, and very short descent and then courses to the right and around the groove to the region of the avascular triangle, posteriorly. Here a branch always courses along the right side of the triangle into the interventricular groove passing down the posterior interventricular groove toward the apex of the heart as the posterior interventricular artry, giving off an average of approximately 2.3 branches to the septum in this region. As previously described, these branches are shorter than those given by the anterior interven-



tricular artery and supply approximately the posterior third of the septum (Figures 1 and 2). In the majority of cases, however, the right coronary passed under the posterior interventricular vein, sending a branch across the top of the posterior interventricular triangle to the left ventricle and supplies an average of 1.8 arteries to the left ventricle posteriorly. As many as six arteries supplying the left ventricle from the right coronary were observed and it was not uncommon to see two or three large arteries crossing the anatomical no-man's land to the left ventricle posteriorly. In the instances when the right coronary crossed the interventricular groove posteriorly, arteries to the left atrium also were observed arising from the transcendent branch. During its course across the right venticle the right coronary artery gave an average of 4.8 branches to the right ventricle.

It was interesting to note that although analyzed separately and using separate slips of paper for the computation of the number of arteries to each part of the heart, the hearts exhibiting right coronary preponderance balance and left coronary preponderance all ended up with the identical average number of arteries to the various chambers of the heart and this rather striking correlation suggested that the left ventricle needed in the realm of approximately twice as much arterial supply as did the right no matter which artery was in size preponderant. This of course is in correspondence with the physiological roles of the two ventricles.

Classification as to Depth of Vessel

In studying the relation of the vessels to the myocardium itself, it was apparent that a distinction could be made. The coronaries may be divided into the *epicardial coronaries* and the *intramuscular coronaries* according to whether they ran on the surface of the heart or were embedded between muscle layers. In general, the *epicardial coronaries* were found to be more tortuous and where atherosclerosis was present, to be involved to a considerable extent; whereas the *intramuscular coronaries* were found to be linear in conformation and to be not subjected to atherosclerosis to the degree as the epicardial coronary. In the case of any given artery descending toward the apex from the atrio-ventricular groove an average of 3.1 convolutions on the right ventricle.

The intramuscular arteries were found to perforate the anterior ventricular groove and run between the muscle layers of the right ventricle and the left ventricle in this locality. Throughout the walls of the ventricle, the vessels perforated the external bulbospiral muscle and ran along the plane of fission between the internal and external bulbospiral following the grain to a great extent. This intramuscular placement of the coursing arteries within the myocardium suggests that the pressure differentials within the arteries themselves would be subject to th rising intramyocardial pressures during systole, whereas the epicardial coronary vessels would be subject to this pressure only as a backflow.

Regarding Atheromas

Fifty-three per cent of the hearts studied exhibited some degree of atheromatosis of the coronary vessel, ranging from the mildest of the

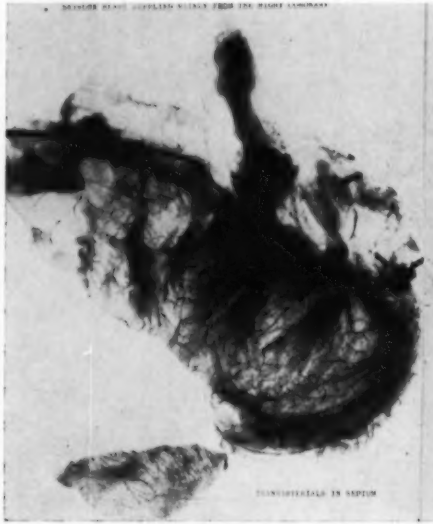


FIGURE 8

FIGURE 9

FIGURE 10

infiltration of the walls with anthomatous material to practically complete occlusion. All vessels which were palpably firm were subjected to an endarterectomy, incising the artery longitudinally to the level of the yellow-appearing material and then using sharp and dull dissection, dissecting the atheromatous portions of the artery from the outer shell. A great variation existed not only in the length of the atheroma but in the character of he atheroma and the thickness of the arterial wall possessed by this process. Some of the atheromata shelled out easily and could be pulled out almost without dissection whereas others required sharp dissection of delicate character for their removal. Still others were for all practical purposes unremovable and their sclerotic and calcific processes involved practically all levels of the arterial wall at some point. Approximately 43 per cent of the vessels were felt to contain atheromata which were segmental and localized enough to be removed in this dissection, whereas the remainder of those in the atherosclerotic group fell into the category of diffuse and unremovable processes. Correlated with age, however, 75 per cent of the latter fell into the age groups over 60 and represented the effects of age and long-standing atherosclerosis.

Coronary Collaterals

In all of the Schlesinger injection studies where atheromatous occlusion was evident it was possible to demonstrate visible coronary collaterals in the films. Some specimens exhibited certain types of collaterals much better than others but in general it appeared that *wherever atherosclerosis occurred one type or other of collaterals appeared.* In those hearts devoid of atheromatous lesions no collateral vessels were noted in our series.

It was possible, by means of their location and function, to classify coronary collaterals into four designations as follows: (1) by-pass collaterals (2) interarterial collaterals (3) transarterial collaterals (4) scar collaterals (neo-angiogenesis) (Fig. 3).

1. *By-pass Collaterals*

Wherever a segmental atheroma occurred it was possible to see dilated channels about the segmental occlusion. In most cases discernable by-pass collateral channel or channels could be made out leading from the unobstructed upper portion of the vessel to the unobstructed lower portion of the vessel (Fig. 4). These were most easily visible where the obstruction was of short length. The term "by-pass collateral" was thought best to describe this variety which brings from the proximal portion of the vessel itself to the distal portion about the obstruction. These were especially prominant in the secondary ventricular arteries but even more dramatic in the atrial region where anastomoses between the primary atrial branches would by-pass a segmentally blocked atrioventricular vessel (right coronary or left circumflex). The importance of these atrial collaterals in the by-passing of obstruction in the main coronary vessels cannot be too greatly emphasized.

2. *Interarterial Collaterals*

Anastomoses occurring between secondary arteries of the same coronary vessel were given the designation of "interarterial collaterals."

These were found in approximately 90 per cent of the instances where atheromas were present and constitute the greater proportion of coronary collaterals (Fig. 6). They vary from rather straight vessels to markedly tortuous vessels and may be seen both in the surface vessels as well as the intermuscular components.

3. *Transarterial Collaterals*

Those vessels extending from the right to the left coronary in the septal region in the posterior interventricular region and sometimes in the anterior interventricular region were designated as "transarterial collaterals" (Fig. 7). These also were quite frequent and occurred in approximately 60 per cent of the instances where atheromas were found. It was particularly gratifying to see to what extent these were found in the septa.

4. *Scar Collaterals*

In those Schlesinger injected hearts which shcwed evidence of myocardial infarction, a fourth type of collateral was distinguishable. These emanated from adjacent vessels near the infarcted area and, quite numerous and intertwining in nature, were found coursing into and through the scarred area. From the nature of their origin and course it was apparent that these were newly developed vessels, not enlargements of previously existing vessels, but spurious vasculature which like in developing scar tissue elsewhere in the body grows in response to necrobiosis. In such areas marked intercommunication and profuseness of the arterial channels is observable in many of the specimens. (Brofman[4] has suggested that during the course of a healing of an infarct the growing new vessels develop both arterial and venous channels which intercommunicate to such a degree that the effect of an arteriovenous shunt is present and has further demonstrated this by catheterization of the coronary sinus during various stages of the healing of a myocardial infarct, obtaining higher values of oxygen saturation particurlarly about the tenth day.)

It was increasingly apparent that, as Schlesinger has indicated, coronary collaterals grow in hearts that are subject to narrowings of the coronary arteries due to atherosclerosis and are a natural compensation mechanism for this disease entity. *The one area where no collateral was evident was in the first few centimeters of the main stem coronary vessels.* Due to the thickness of the walls of the vessels and a lack of adjacent musculature, no opportunity for the enlargement of existing microscopic or small vessels is present. It is in this area that remedial surgical steps are most promising.

SUMMARY

A classification of coronary arteries is suggested using the terms atrio-ventricular vessels and intraventricular vessels which are more indicative of their localization and function. The location of the coronary orifices above the leaflets of the aortic valve was clarified and the location of the orifices in regard to the anterior posterior axis was found to be quite variable. Classification of intercoronary collaterals is suggested, namely, by-pass collaterals, interarterial collaterals and transarterial collaterals which were found had developed as atheromas formed in the various parts of the coronary tree. A fourth type of collateral, scar collaterals or neo-angiogenesis, is discussed. The role of the atrial vessels as carriers of collateral circulation about the atrio-ventricular occluded vessels is emphasized.

ACKNOWLEDGEMENT: Acknowledgements to Dr. John J. Sampson who initiated the program of Schlesinger Injections at Mt. Zion Hospital, to Dr. Gerson R. Biskind, under whose direction the injections and skiagrams were prepared. To Louise Horn, medical illustrator, for conscientious and painstaking work. To Doctors Milton Pearl, Morris Culiner and others who over a period of years prepared the injected specimens.

RESUMEN

Se sugiere una clasificación de las arterias coronarias, usando los términos vasos atrioventriculares y vasos intraventriculares, que son mas indicadores de su localización y de su función. La ubicación de los orificios coronarios arriba de las hojuelas de la válvula aórtica se aclaró y las localizaciones del orificio respecto de la posición anteroposterior del axis se encontró que es bastante variable. Se sugiere la clasificación de colaterales intercoronarias, por ejemplo colaterales de desviación, colaterales interatriales y colaterales transarteriales que se encontró se desarrollan cuando el ateroma se desarrolla en varias partes del árbol coronario. Se diserta sobre un cuarto tipo de colateral, las colaterales cicatriciales o por neoangiogénesis. El papel de los vasos atriales como conductores de circulación colateral alrededor del atrioventricular ocluído se destaca.

RESUMÉ

L'auteur suggère une classification des artères coronaires, en utilisant les termes de "vaisseaux atrio-ventriculaires et vaisseaux intraventriculaires" qui donnent une indication plus précise de leur localisation et de leur fonction. Le siège des orifices coronaires au-dessus des valvules de la valve aortique a été déterminé et le siège des orifices par rapport à l'axe antérieur-postérieur a été trouvé être assez variable. L'auteur suggère une classification des collatérales intercoronaires, c'est-à-dire collatérales anastomotiques, collatérales interartérielles et collatérales transartérielles, qui furent trouvées comme développées par l'athérome dans les différentes parties de l'arbre coronarien. Un quatrième type de collatérale, les collatérales cicatricielles ou de néo-vascularisation, est discuté. Le rôle des vaisseaux auriculaires comme véhicules de la circulation collatérale après occlusion des vaisseaux auriculo-ventriculaires est mis en évidence.

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Physiologic Evaluation of Angina Pectoris*

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Electrocardiographic and ballistocardiographic observations have been the only objective methods easily available for assessment of the state of the coronary circulation. As has been pointed out, however, these methods give only indirect information concerning the hemodynamic status and functional adequacy of the coronary circulation.

The extensive pathologic studies of the coronary arteries in angina pectoris[1,2] have demonstrated that these vessels seldom show a single vascular disturbance, but more often, demonstrate diffuse involvement of the entire coronary vascular tree leading to increased large vessel resistance to blood flow.

Physiological principles have been applied to the understanding of other cardiac problems, particularly valvular, congenital and constrictive heart disease and congestive heart failure. They have led to the development of objective hemodynamic methods of evaluation which would appear to be of value for the coronary circulation as well. We have attempted such an approach.

Our findings are based on a correlative clinical, electrocardiographic and cardiac catheterization study of 43 patients. Coronary sinus catheterization was performed and coronary blood flow measured by the nitrous oxide technique[3] as modified by Goodale and Hackel.[4] Diastolic coronary vascular resistance was calculated.[5] The group of 43 patients was subdivided as follows:

Group 1 was the normal group, composed of 10 patients with negative histories, physical examinations and resting and post-exercise electrocardiograms.

Group 2 was the abnormal group, composed of 23 patients with typical angina pectoris and positive electrocardiographic examinations.

Group 3 was designated the unknown group, composed of 10 patients, all of whom complained of atypical chest pain, and in whom the resting and exercise electrocardiograms were negative or equivocal. Three of these patients had left ventricular hypertrophy secondary to aortic valve disease.

The open columns in Figure 1 summarize the results of resting studies performed in normals, in patients with coronary artery disease and in those with increased left ventricular work. Coronary flow was essentially the same in all three groups; in the coronary group it was actually 19 per cent above normal. Diastolic coronary vascular resistance, which encompasses coronary inflow time as well as perfusion pressure, is perhaps the most useful index of the cross-sectional area of the coronary vascular bed. Again, no difference was found among these groups.

In a recent report[6] evaluating internal mammary ligation for angina pectoris, nitrous oxide flows were performed at rest. The authors found no difference in values before and after ligation, and therefore, concluded

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that the procedure was of no value. It would seem to us that a coronary flow functionally adequate to maintain viability at rest should not necessarily be expected to increase post-operatively unless resting flow were inadequate or unless the demands on the systemic circulation were increased. Conclusions based on flow measurements made at rest are of little value, particularly when one considers that the symptoms of the disease being studied are precipitated by stress. Many investigators have shown that evaluation of organ systems with large functional reserve capacities by static resting determinations is incomplete. Dexter's group[7] in their studies on ventricular failure; Master[8] in his electrocardiographic investigation of coronary artery disease; and Thorn,[9] utilizing the ACTH test in the study of adrenal capacity, have emphasized the importance of a stress situation in the dynamic evalution of function.

Should one then actually expect a low resting coronary flow in angina pectoris? Since oxygen extraction is near maximal at rest in the coronary capillaries, a decrease in coronary flow as coronary arterial obliteration progresses could only lead to a decreased myocardial oxygen consumption. Cardiac work, however, is usually normal or even greater than normal in patients with angina pectoris. It seems highly unlikely that this diseased myocardium would now require less oxygen for the same basal work or resort to chronic anaerobic metabolism — an inefficient process of energy production. Gregg[10] points out that myocardial hypoxia leads immediately to coronary vasodilatation. Flow is thus maintained. With progressive vascular disease, this vasodilatory reserve keeps coronary flow to viable muscle normal. This reserve is eventually exhausted and flow can no longer increase on demand. At rest there is little difference in measured flow between the normal group with a large, *as yet unused,* reserve capacity and the angina pectoris group in which the

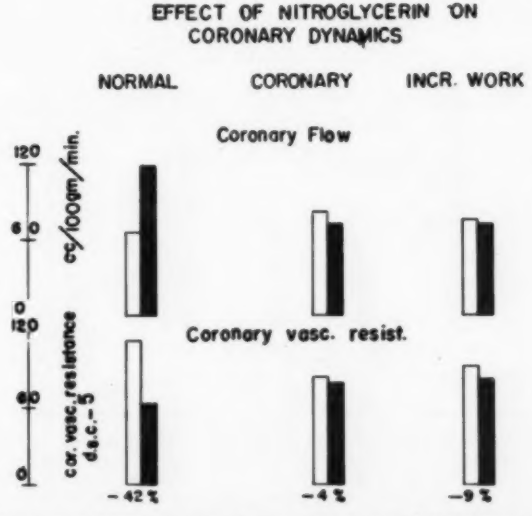

FIGURE 1: The open columns represent coronary flow and diastolic coronary vascular resistance in the normal, coronary artery disease and increased left ventricular work groups at rest — the black columns during the effect of nitroglycerin.

measured flow actually represents the result of nearly maximal vascular dilatation.

Improvement in the coronary circulation, whether by drugs or by surgical procedures, can only be shown by demonstrating a *reserve* capacity increased over the pre-treatment state. Some form of stress can determine how extensive this reserve is. We have used this approach to study two clinical problems: 1) the evaluation of atypical chest pain; 2) the objective assessment of surgical therapy for angina pectoris. Our observations were made at rest and then repeated following one of two challenges to coronary dilatation — either nitroglycerin or exercise.

Figure 2 illustrates the effect of nitroglycerin on coronary flow and diastolic coronary vascular resistance. In our normal group there was an average 63 per cent increase in coronary flow with a 50 per cent decrease in coronary vascular resistance, demonstrating a reserve capacity for vasodilatation. In the presence of coronary artery disease with angina pectoris, coronary blood flow changed little after nitroglycerin, and coronary vascular resistance was virtually fixed. The striking difference among the groups may be explained by exhaustion of dilatory reserve in the angina group. This difference in reactivity between the normal and diseased coronary circulation has been used in the evaluation of patients with atypical chest pain in whom negative or equivocal electrocardiographic findings could lead to only presumptive diagnoses of coronary arteriosclerosis. Three patients from this group are presented.

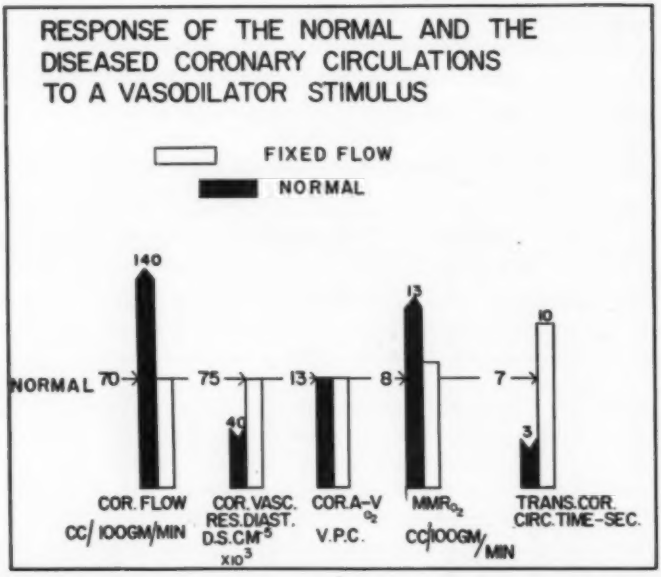

FIGURE 2: Coronary flow in the normal group increased 63 per cent with concomitant 50 per cent decrease in diastolic coronary vascular resistance following a challenge to vasodilatation. In the fixed flow group, there was no change in coronary flow, diastolic coronary vascular resistance, arteriovenous oxygen content or metabolic rate for oxygen (myocardial oxygen consumption [MM RO_2]), all of which remained at resting levels. The transcoronary circulation time was shortened in the normal group in response to the stimulus to vasodilatation. In those patients with fixed flows, the transcoronary circulation time was prolonged after nitroglycerin.

TABLE 1— EFFECT OF SURGICAL REVASCULARIZATION PROCEDURES ON CORONARY CIRCULATION

		Coronary Flow		Diastolic Coronary Vascular Resistance		
		cc/100 gm/min		dyne sec cm^{-5} (x 10^3)		
PHENOL DE-EPICARDIALIZATION		rest	tng	rest	tng	Relief
M.K.	before	—	—	—	—	
	after	81	69	70	77	1 year
St.M.	before	93	85	61	49	4 mos.
	after	84	64	65	86	uses tng
INTERNAL MAMMARY LIGATION		rest	effort	rest	effort	
R.F.	before	—	—	—	—	
	after	50	63	83	78	6 mos.
J.P.	before	—	—	—	—	
	after	85	78	70	70	none

tng = nitroglycerin

The patient illustrated in Figure 3 was a 39 year-old housewife who complained of exertional chest pain with an atypical locus (point of maximal impulse). On physical examination blood pressure was 150/60 and the murmur of aortic insufficiency was heard. Her electrocardiogram showed left ventricular hypertrophy; the Master's test was negative. Coronary flow studies revealed a 40 per cent increase in flow with a concomitant 33 per cent decrease in diastolic coronary vascular resistance following nitroglycerin administration. This patient clearly possessed a coronary reserve capacity available in response to increase demand for flow. We were unable to demonstrate objective evidence of significant coronary artery disease.

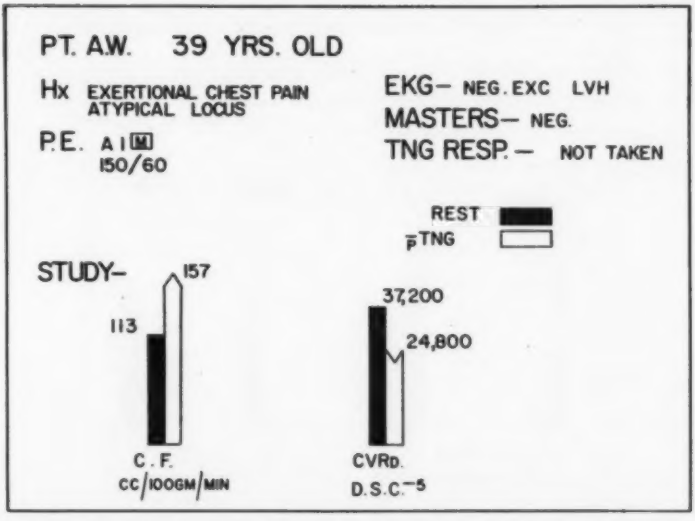

FIGURE 3: Coronary flow measurements in a 39 year-old woman with atypical chest pain. See text.

In Figure 4 two patients presenting with essentially similar complaints and physical findings are compared. Both had angina pectoris. In L. F., nitroglycerin afforded some clinical relief; in F. M., prior to aortic valvuloplasty, nitroglycerin provided little or no alleviation from pain. On physical examination, their blood pressures were unremarkable; both showed systolic and diastolic murmurs at the base and left sternal border. In L. F., the electrocardiogram was negative; in F. M., there was left ventricular hypertrophy. In both cases, the Master exercise tests were negative. Both had left heart catheterizations which revealed an aortic valve gradient of 20 mm. Hg. In L. F. the aortic valve calculated to 1.0 cm^2; in F. M., to 0.8 cm^2. Coronary flow studies were performed at rest and following a challenging dose of nitroglycerin. L. F. showed a fixed coronary flow and diastolic coronary vascular resistance — there was no detectable coronary dilating reserve remaining. The positive finding of a fixed flow was extremely helpful in our therapeutic approach. The work of the heart has been decreased by I^{131} induced hypothyroidism in order to adjust demand to available coronary flow. The patient has been clinically improved now for one year. F. M. increased his coronary blood flow by 42 per cent and his coronary vascular resistance showed a concomitant decrease of 57 per cent. These studies, performed post-operatively after aortic valvuloplasty, illustrate a normal ability to dilate. Severe aortic valvular disease thus seemed to have been the most important etiologic factor in the production of his angina pectoris by requiring a higher coronary flow. With reduction in valvular gradient and a decrease in left ventricular work, less oxygen was needed by the myocardium and, hence, less coronary flow. As a result, when the coronary bed constricted following surgery, he regained some coronary vascular reserve. Post-operatively, (although open to subjective variation) there was

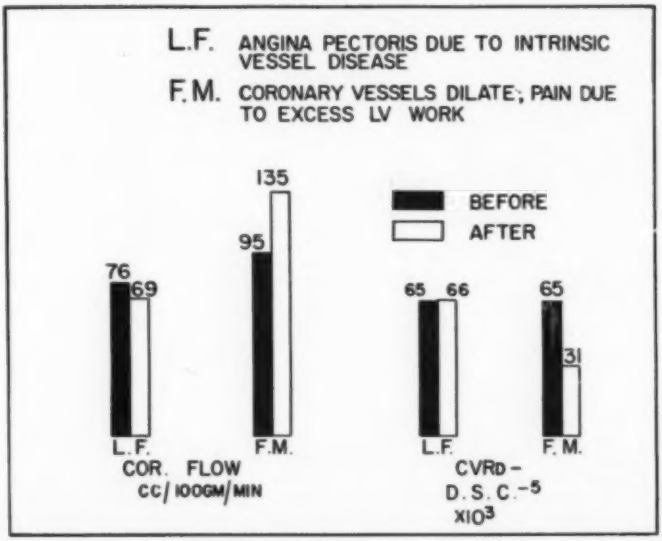

FIGURE 4: See text.

a marked decrease in the number of anginal attacks and particularly in the amount of effort needed to produce them.

In another group of patients with angina pectoris, coronary flow determination was repeated after coronary reserve was challenged by a standard exercise test. In every instance in which clinical pain was induced, coronary blood flow was found to be inadequate to meet demand.

Figure 5 illustrates the findings in one patient who developed pain and electrocardiographic changes consistent with a diagnosis of coronary insufficiency. The white columns represent the values for both normal and angina pectoris patients at rest. As noted previously, there is no essential difference between these groups in the resting state. The dotted portion indicates the normal response to effort and the black column, the response found in this patient with angina pectoris. The coronary flow, instead of arising on effort, as seen in the normal group, was virtually fixed — there was only a 10 per cent fall in coronary vascular resistance and a marked fall in coronary venous oxygen content. Coronary venous pyruvate and lactate levels rapidly rose above arterial values in the angina group (no change in the normal group) as the myocardium, having exhausted available oxygen reserves converted to anerobic glycolysis.

We have applied these methods of evaluation to two surgical procedures commonly utilized in the therapy of angina pectoris. Results of preliminary studies on four patients are shown in the Table. The first two patients were treated by epicardial phenolization, poudrage and

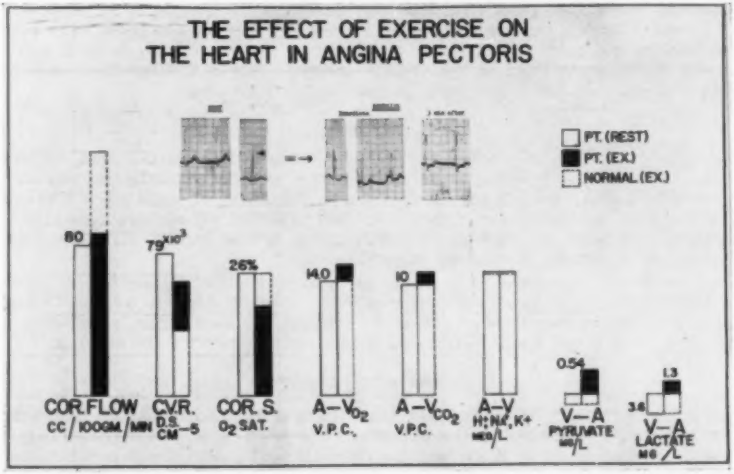

FIGURE 5: Discussion in text. The ECG demonstrates the acute ST segment depression recorded following the inception of anginal pain at the time of the physiological studies. The white columns represent values for both the normal and angina pectoris patients at rest, indicating all physiologic and biochemical parameters were normal at rest. The dotted portion indicates the possible normal response to effort and the black column, that in angina pectoris. The dotted values below the baseline for pyruvate and lactate indicate *utilization* of these substances at rest; values *above* the baseline indicate *production*.

cardiopneumopexy; in the second two, the internal mammary arteries were ligated bilaterally. Three showed marked relief of angina ranging from four months to one year. One had no relief following the procedure. One was studied in the pre and post operatively state; three were studied post-operatively only. In the first two patients, nitroglycerin was the challenge to dilatation; in the second two, an exercise stimulus was utilized. None of the patients studied revealed significant increases in coronary flow or decrease in coronary vascular resistance following a stress challenge. Indeed, several appeared to have less reserve following the procedure than they did prior to its performance. Similarly, no electrocardiographic improvement occurred after surgery. It would seem that neither operation significantly improved coronary reserve capacity.

SUMMARY

The armamentarium presently available for the diagnosis of chest pain includes the patient's history and physical examination and the electrocardiogram at rest and following effort. In equivocal cases, and particularly in evaluation of medical and surgical therapy, physiological study of the coronary circulation is essential. We have found this to be a safe, although not a simple procedure.

The crucial question in any study of the coronary circulation is: can the coronary vascular bed dilate to accept more blood flow on demand? A fixed or inadequate flow response would appear to indicate coronary insufficiency and may serve as an objective physiologic method of evaluation.

RESUMEN

Los medios de diagnóstico actualmente asequibles para el dolor torácico, incluyen la historia clínica, el examen físico y el electrocardiograma en reposo y después del esfuerzo.

En casos dudosos y en especial para valorar el tratamiento médico o quirúrgico, es esencial el estudio fisiológico de la circulación coronaria. Encontramos que es un procedimiento seguro aunque no es sencillo.

La cuestión crucial en cualquier estudio de la circulación coronaria es: ¿Puede el lecho vascular coronario dilatarse para recibir mas sangre en caso de exigencia? Una respuesta de inmutabilidad o inadecuada, parece indicar insuficiencia coronaria y puede servir como un método objetivo de estimación fisiológica.

RESUMÉ

L'équipement actuellement utilisable pour le diagnostic des douleurs thoraciques comprend l'histoire du malade, l'examen physique, et l'électrocardiogramme au repos et après effort. Dans les cas suspects, et particulièrement lorsqu'il s'agit d'évaluer la nécessité d'une thérapeutique médicale ou chirurgicale, l'étude physiologique de la circulation coronaire est essentielle. Nous avons trouvé qu'elle était sans danger, encore que ce ne soit pas un procédé simple.

La question cruciale dans toute étude de la circulation coronaire est: le lit vasculaire coronarien peut-il se dilater pour recevoir un débit sanguin augmenté selon la demande? Un débit stable ou inapproprié semblerait indiquer une insuffisance coronarienne et peut servir comme méthode physiologique objective d'évaluation.

ZUSAMMENFASSUNG

Das gegenwärtig zur Verfügung stehende Rüstzeug zur Diagnostik bei Brustschmerzen umfaßt die Vorgeschichte des Kranken, die physikalische Untersuchung, sowie des Elektrokardiogramm in Ruhe und nach Belastung. In zweifelhaften Fällen-und besonders wenn interne oder chirurgische Therapie in Erwägung gezogen wird,-ist eine physiologische Untersuchung des Coronarkreislaufes wesentlich. Wir fanden, daß dies eine zuverlässige, wenngleich nicht einfache Methode darstellt.

Die kritische Frage bei jeder Untersuchung des Coronarkreislaufes ist diese: können sich die Coronargefäße so erweitern, daß sie bei Bedarf eine stärkere Durchströmung zulassen? Eine starre oder inadäquate Durchströmung bein entsprechenden Anforderungen dürfte einer Coronarinsuffizienz gleichkommen und als objektives physiologisches Auswertungsverfahren dienen.

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Clinical Experience with Elixophyllin in Dyspnea

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Dyspnea may be a symptom of pulmonary or cardiac disease or both. In the dyspnea of cardiac origin, digitalis is generaly considered specifcally indicated. However, in some circumstances digitalis may provide little or no relief of cardiac dyspnea. In early failure when there are no physical signs of congestion, relief of dyspnea is unimpressive and equivocal. In frank failure, digitalis helps in remission of major signs and symptoms, but some exeetional dyspnea usually semains.[1]

Diuretics sometimes offer additional help in these cases. However, there is need for more effective drug therapy for relief of dyspnea, orthopnea, fatigue, wheezing and coughing which persists in many of these patients. These symptoms tend to make the patient morbid, fearful and so restricted in activity that he may be virtually a "cardiac invalid." In older patients with congestive failure complicating chronic asthma, bronchitis or bronchospastic pulmonary emphysema, the dyspnea may be of combined cardiac and pulmonary origin.

From pharmacologic considerations, theophylline would appear to be an ideal drug for these patients. It increases the pulmonary circulation, especially when the lungs are congested from left ventricular failure. In patients in congestive failure, theophylline shortens abnormally prolonged circulation time and decreases venous pressure.[2]

Clinically, aminophylline (theophylline ethylenediamine) administered intravenously is usually effective for relieving the paroxysmal dyspnea of congestive failure, acute bronchial asthma, Cheyne-Stokes respiration and pulmonary edema.[3]

The prophylactic use of aminophylline orally or rectally to prevent dyspnea, especially that of cardiac origin, has been rather unsatisfactory. Occasionally the drug is of benefit, but it is often disappointing.

Theophylline blood-level data indicate that the source of this disappointment lies in the uncertain absorption of aminophylline administered orally or rectally. By mouth, gastric intolerance generally limits oral doses to inadequate amounts. By rectum absorption may be comparatively rapid, it may be delayed for many hours or there may be no detectable theophylline in the blood-stream at any time after administration.[4]

More recently, a hydroalcoholic solution of theophylline (Elixophyllin®) has been reported to be well tolerated, and rapidly and completely absorbed after oral administration. In 15 minutes following oral administration in doses equivalent to 500 mg. of aminophylline, the mean blood level was 8.0 mcg/ml. (higher than the 7.0 mcg/ml. following intravenous aminophylline, 300 mg.). Moreover, absorption appeared to be essentially complete and showed less patient variation. The mean peak blood level was reached in one hour. All patients had blood levels over 5.0 mcg/ml. at that time.[5]

®Sherman Laboratories, Detroit, Michigan.

During the past two years Elixophyllin has been studied rather extensively in bronchial asthma. Following its administration, 85 of 107 acute asthmatic attacks were termniated in 10 to 30 minutes.[8,9] Greater relief of chronic bronchial asthma has been reported.[10,11,12] More predictable absorption and better maintenance of therapeutic blood levels is responsible for better clinical results.

It appeared that this preparation might be helpful in the dyspnea of cardiac origin unrelieved by digitalis; bronchospastic pulmonary emphysema and chronic asthma with or without cardiac involvement. This is a report of the clinical experience gained in such cases.

Method and Material

The study included 10 cases of cardiac asthma, four of bronchial asthma and five of chronic obstructive emphysema. The ages of these patients ranged between 35 and 70 years.

Most of the patients have had other drugs including aminophylline by mouth. Some have had aminophylline per rectum. In these patients dyspnea, orthopnea, fatigue, wheezing and coughing were prominent clinical symptoms.

Patients were started on Elixophyllin, four tablespoonfuls four times a day. This dose was gradually reduced to a maintenance dose of one tableespoonful four times a day. The follow-up on individual patients varied from five to eight months.

Results of the study are summarized in the following table.

TABLLE 1—RESULTS OBTAINED IN PATIENTS TREATED WITH ELIXOPHYLLIN

Diagnosis	Number of Patients	Duration of Treatment (months)	Results Satisfactory	Unsatisfactory	Side Effects
Cardiac Asthma	10	4-6	80%	20%	1 case nausea 1 case nausea and heartburn
Bronchial Asthma	4	2-3	75%	25%	none
Emphysema	5	4-6	80%	20%	1 case of nausea

Discussion

Eight of 10 patients with cardiac asthma received good to excellent results from Elixophyllin therapy. One complained of nausea and discontinued its use. Another received limited benefit. One complained of nausea and heartburn in the beginning which was prevented on administration of an antacid. Satisfactory results essentially without side effects were seen in eight cases. The duration of treatment in cases of cardiac asthma was four to six months.

Three of four bronchial asthmatic patients showed excvellent response. The clinical response in one case was equivocal. No side effect was present in these patients. The duration of treatment was two to three months.

Five emphysema patients were treated for four to six months. One complained of slight nausea but he continued the medication with good clinical results. Another di not receive satisfactory results. Good to excellent results were seen in four of five patients.

In the three groups of patients, satisfactory results were obtained in 15 of 19 cases. Results in two were equivocal. One complained of nausea and heartburn and two of nausea. No other side effect was present.

The one who had previously received aminophylline by mouth or by rectum provided a basis for comparison with Elixophyllin. Faster, greater and more consistent relief was obtained with Elixophyllin. The patient-acceptability of Elixophyllin was excellent except for a few complaints of nausea and heartburn after initial administration of Elixophyllin. This was prevented by use of antacids.

Discussion of two representative case histories will be of interest.

A woman, 45 years of age, had hypertensive heart disease and mitral regurgitation for nine years. Her major symptoms were dyspnea, orthopnea and fatigue on the slightest exertion and marked wheezing and coughing. The x-ray examination showed an enlargeemnt of her heart both to the left and to the right. There was some pulmonary congestion involving both lung fields. Other general findings were essentially negative. Complete blood count was normal. Urinalysis was normal. ECG showed left ventricular preponderance. She was on digitalis and diuretics for a number of years. In addition, she had been tried on various xanthine combinations, namely aminophylline, theominal, Theocalcin and tedral. All these drugs have helped her to be more comfortable, but until she was put on Elixophyllin she did not walk as far or walk as much and feel as well. She has been on this drug now for si xmonths. The dose of Elixophyllin required to achieve this effect is one tablespoonful four times a day. In the beginning, she started on four tablesepoonfuls four times a day and gradually reduced where she is now maintained on one tablespoonful four times a day.

A man, 55 years old, had been known to have mitral regurgitation with stenosis for the last six years. He entered the hospital with cyanosis, orthopnea, dyspnea and pulmonary edema. His general condition was poor and he was critically ill. His condition continually worsened in spite of oxygen, aminophylline intravenously, digitoxin and diuretics, namely 2 cc. of Thiomerin, three times a week. His ECG showed coronary changes. His chest x-ray films revealed left ventricular preponderance with pulmonary edema. After 10 days on chlorothiazine 1 gram daily, he started to improve. Pulmonary congestion was relieved by the diuretics, but symptoms of coughing and wheezing continued unabated. He was unable to retain aminophylline suppositories. Meticorten 5 mg. q.i.d. for two weeks was administered. Steroid therapy provided some relief, but eventually in spite of the diuretics given, it produced salt retention and was discontinued. After two days, he was put on Elixophyllin, four tablespoonfuls four times daily. There was immediate marked improvement of dyspnea, orthopnea and wheezing. This man was kept on a regimen of one tablespoonful four times a day for two months. He responded favorably. Wheezing stopped and coughing subsided. He continued to take Elixophyllin p.r.m. for dyspnea and orthopnea.

SUMMARY

A newe oral preparation of theophylline (containing 80 mg. of free theophylline and 3 cc. of ethyl alcohol per 15 cc.) provides faster, more complete and more dependable absorption than other oral theophylline preparations hitherto available. In some cardiac patients, dyspnea, orthopnea, fatigue, wheezing and coughing often persist despite full idgitalization. Good to excellent relief of these symptoms was secured with Elixophyllin in eight of 10 such cardiac patients; in three of four patients with chronic bronchial asthma and in four of five with pulmonary emphysema.

RESUMEN

Una preparación nueva de teofilina oral (conteniendo 80 mg. de teofilina libre y tres cc. de alcohol etílico por 15 cc.) proporciona una absorción más rápida y segura que otras preparaciones hasta ahora obtenibles. En algunos enfermos cardiacos, la disnea, ortopnea, fatiga, silbidos y tos, persisten a menudo a pesar de la digitalización. Se obtiene buen alivio o excelente de estos síntomas con la Elixofilina en 8 de 10 de tales casos de cardiacos; en tres de cuatro enfermos con asma bronquial crónica y en cuatro de cinco con enfisema pulmonar.

RESUMÉ

Une nouvelle préparation buccale de théophylline (contenant 80 mg. de théophylline libre et 3 cc. d'alcool éthylique pour 15 cc.) permet une absorption plus rapide, plus complète et plus efficace que les autres préparations buccales de théophylline dont on a disposé jusqu'à présent. Chez quelques malades cardiaques, la dyspnéa, l'orthopnéa, la fatigue, le "wheezing" et la toux persistent souvent malgré une digitalisation complète. Chez de tels cardiaques, un bon soulagement allant jusqu'à un soulagement parfait de ces symptômes fut obtenu avec l' "Elixophylline"; le même résultat fut obtenu pour trois sur quatre malades atteints d'asthme bronchique chronique, et pour quatre sur cinq malades atteints d'emphysème pulmonaire.

ZUSAMMENFASSUNG

Ein neues orales Theophyllin-Präparat, das mg freies Theophyllin und 3 ccm Äthylalkohol auf 15 ccm enthält, führt gegenüber anderen oralen bisher zur Verfügung stehenden Theophyllin-Präparaten zu einer schnelleren, vollzständigeren und zuverlässigeren Absorption. Bei manchen Herzkranken bleiben trotz voller Digitalisierung Dyspnoe, Orthopnoe, Müfigkeit, Pfeiffen beim Atmen sowie Husten oft bestehen. Gute bis ausgezeichnete Linderung dieser Symptome wurde mit Elixophyllin bei 8 von 10 solcher Herzkranken erreicht; ebenso bei 3 von 4 Kranken mit chronischem Bronchialasthma und bei 4 von 5 Kranken mit Lungenemphysem.

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A Comparison of the Effectiveness of Parenteral Digoxin and Lanatoside C

Parenteral digitalization is often required for the therapy of acute pulmonary edema and the control of ectopic atrial rhythms. In these instances, the selection of an appropriate digitalis glycoside depends on the rapidity of action of the parenteral drug. Lanatoside C (Cedilanid) and ouabain are especially valuable in this regard. The usefulness of ouabain is limited, however, by the narrow range which exists between its therapeutic and toxic effects; and the short duration of lanatoside C precludes its use for long-term administration. In contrast, digoxin is a rapid-action glycoside with a more prolonged cardiotonic effect. Therefore digoxin may be effectively utilized both for rapid digitalization and maintenance therapy. The present study compares the effectiveness of parenteral digoxin and lanatoside C in the control of atrial fibrillation.

Material and Methods

Thirty patients with atrial fibrillation were studied. In each instance, the ventricular rate was greater than 100 per minute. Fifteen subjects had received prior digitalis therapy; the other 15 had not been previously digitalized.

Among the previously undigitalized group, 10 were treated with intravenous digoxin* and five with lanatoside C. The initial digoxin dosage was 1.0 mg. Thereafter 0.5 mg was administered every two hours until the ventricular rate fell below 100 per minute. The initial intravenous

*Kindly supplied by Burroughs Wellcome and Company.

TABLE 1—PREVIOUSLY UNDIGITALIZED PATIENTS WITH ATRIAL FIBRILLATION

Patient	Drug	Total Dosage (mg)	Time Required To Slow Ventricular Rate<100/min (hrs)	Time Required To Convert To Normal Sinus Rhythm (hrs)*
1. T. M.	Digoxin	1.5	3	—
2. E. N.	Digoxin	1.5	3½	10
3. S. S.	Digoxin	1.5	3	7
4. M. H.	Digoxin	1.0	1½	1½
5. G. R.	Digoxin	1.5	4	—
6. J. M.	Digoxin	1.0	2	—
7. T. V.	Digoxin	1.0	2½	14
8. M. B.	Digoxin	1.5	3	—
9. O. T.	Digoxin	1.0	2	2
10. L. K.	Digoxin	2.0	6	—
11. H. H.	Lanatoside C	0.8	3	—
12. E. H.	Lanatoside C	1.2	4	—
13. R. C.	Lanatoside C	1.6	5½	8
14. E. L.	Lanatoside C	1.2	3½	—
15. L. S.	Lanatoside C	1.2	4	6

*Observation limited to 24 hours

dose of lanatoside C was 0.8 mg and additional 0.4 mg increments were injected at two-hour intervals until the apical rate slowed below 100.

Ten previously digitalized subjects were treated with digoxin and five with lanatoside C. In the latter group, the initial digoxin dose varied from 0.5 to 0.75 mg. Thereafter 0.25 mg was injected every two hours until the ventricular rate fell below 100. The initial dosage of lanatoside C varied from 0.4 to 0.6 mg and then 0.2 mg was given at two-hour intervals until the ventricular response was adequately slowed.

Findings

The dosage of digoxin and lanatoside C and the time required to slow the ventricular rate below 100 per minute are listed in Tables 1 and 2. Among the previously undigitalized patients, the average digoxin requirement was 1.35 mg and the apical rate was controlled in three and one-half hours. The average dosage of lanatoside C was 1.16 mg and four hours were required to slow the ventricular response.

In the digitalized group, the additional digoxin requirement averaged 0.8 mg and the dosage of lanatoside C was 0.92 mg. The average time required to slow the ventricular rate was 3.15 hours with digoxin and 4.40 hours with lanatoside C. Those instances in which the atrial fibrillation converted to normal sinus rhythm are also listed in Tables 1 and 2.

Discussion

The effect on the heart is essentially the same with each of the digitalis glycosides.[1] The differences encountered are quantitative and are related to speed and degree of absorption and variability in duration of action. Digoxin and lanatoside C both have a rapid onset of action; however the effect of the former drug is much more prolonged.

The rapidity of action of digoxin has been gauged in previous studies[2,3] by the onset of ventricular slowing in patients with atrial fibrillation. After intravenous injection, an effect has been noted within five to 10 minutes. When full digitalization was achieved, the digitalis effect was sustained for five to seven days. Lanatoside C manifests its initial action within 10 to 30 minutes; however its effect is maintained only 16 to 32 hours.[4,5]

The rapid dissipation of lanatoside C makes it unsuitable for oral administration. In contrast, digoxin is longer-acting and therefore oral digoxin may be effectively

TABLE 2—PREVIOUSLY DIGITALIZED PATIENTS WITH ATRIAL FIBRILLATION

Patient	Drug	Total Dosage (mg)	Time Required To Slow Ventricular Rate<100/min (hrs)	Time Required To Convert To Normal Sinus Rhythm (hrs)*
1 A. B.	Digoxin	1.0	3	—
2. T. J.	Digoxin	0.75	3½	—
3. L. M.	Digoxin	0.75	4	—
4. P. M.	Digoxin	0.75	2	—
5. E. E.	Digoxin	1.0	6	24
6. F. L.	Digoxin	0.75	4	—
7. N. M.	Digoxin	0.75	2	—
8. G. C.	Digoxin	0.50	1	12
9. D. S.	Digoxin	1.0	2	—
10. A. P.	Digoxin	0.75	4	4
11. R. D.	Lanatoside C	0.6	3	—
12. F. F.	Lanatoside C	0.8	2	—
13. D. M.	Lanatoside C	0.8	4	—
14. J. V.	Lanatoside C	1.2	7	—
15. A. M.	Lanatoside C	1.2	6	—

*Observation limited to 24 hours

used for maintenance therapy. Lown and Levine state: "If one digitalis agent were to be recommended for its adaptability to the many and varied clinical contingencies, we believe digoxin would be the drug of choice."[1]

The present study confirms the clinical usefulness of parenteral digoxin. The comparative effectiveness of intravenous digoxin and lanatoside C are similar.

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Varying Paroxysmal Atrial Tachycardia with Block, Atrial Fibrillation, Nodal Rhythm and Changing Atrial Pacemaker

The tracings are those of a 17-year-old girl who had primary suture of a cribriform atrial septal defect without use of a sponge prosthesis during the total cardiopulmonary by-pass.

The first tracing represents the patient's pre-operative electrocardiogram with normal sinus rhythm existing. A right-sided conduction defect which persisted throughout her subsequent course is seen.

EKG No. 2 was taken 1 day post-operative after the patient had received 1.2 mgm. digitoxin and had been placed on a daily maintenance of 0.1 mgm. The rhythm is that of paroxysmal atrial tachycardia (PAT) with block alternating with normal sinus rhythm.

Tracing No. 3 was recorded on the fourth post-operative day, the patient still receiving 0.1 mgm. daily of digitoxin. A supra-ventricular tachycardia has been established.

On the seventh post-operative day, after two days of an increased digitoxin maintenance of 0.2 mgm. daily, the patient received 0.6 mgm. digitoxin in divided doses in an attempt to break her tachycardia and establish normal sinus rhythm. This schedule was repeated the following day at the time of EKG No. 4, which again shows PAT with block.

On the ninth post-operative day, after digitalis had been withdrawn, quinidine was started, and at the time of tracing No. 5, 3.6 gm. had been given over a two-day period. Supra-ventricular tachycardia was again seen, but subsequent records the same day demonstrated reversion to the pattern seen in the previous tracing.

After having received daily doses of quinidine as recorded in Table 1, the patient was complaining of nausea and tinnitus, and the medication

TABLE 1

Post-op. day	Digitoxin mgm/day	Quinidine gm/day	EKG No.
—1	0.6	—	1
0	0.6	—	—
1-4	0.1	—	2, 3
5, 6	0.2	—	—
7, 8	0.6	—	4
9	0.2	1.2	—
10	0.2	2.4	5
11	—	2.5	—
12	—	2.0	—
13, 14	—	—	6
15, 16	0.6	—	—
17	0.4	—	—
18, 19	0.6	—	7
20	0.4	—	8, 9
21-28	—	—	10, 11

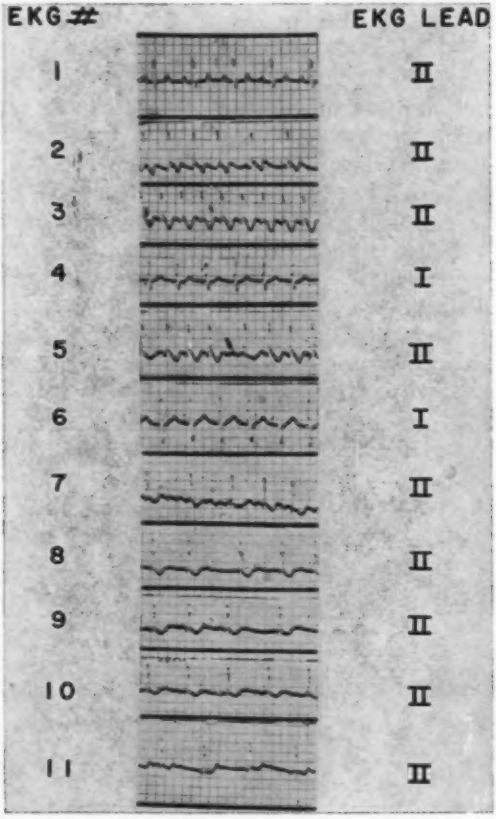
was stopped. EKG No. 6, taken on the 13th post-operative day, continued to show PAT with block.

When digitalis had previously been discontinued, it was felt that the PAT with block might possibly represent digitalis toxicity. Inasmuch as no EKG change was noted after stopping digitalis and inducing quinidine toxicity, it was decided to pursue digitoxin therapy until either a change in the cardiac rhythm or toxicity occurred.

Accordingly, the patient was re-started on digitoxin, 0.2 mgm. every six hours, on the 15th post-operative day. No EKG change was noted until tracing No. 7 on the 18th post-operative day, when a pattern of supra-ventricular tachycardia of flutter-fibrillation variety had been established.

Progressive slowing of cardiac rate was noted until the patient became nauseated, suggesting digitoxicity after 3.2 mgm. digitoxin given over a 6-day period. Tracing No. 8 demonstrates this and pure atrial fibrillation.

Following withdrawal of all drugs, the EKG reverted to a mixture of normal sinus and nodal rhythms on the 21st post-operative day, as seen in EKG No. 9. Six hours after this latter tracing, it was noted that the patient's P-waves had inverted (tracing No. 10), indicating retrograde conduction from a nodal focus.



Finally, a nodal rhythm with impulses arising at varying foci in the node was established as seen in the final EKG. This rhythm remained constant until the patient's discharge from the hospital 5 days later.

These tracings demonstrate abnormalities in cardiac rhythm which occurred immediately following primary suture of a large atrial septal defect, and were unaffected by moderate amounts of digitalis and toxic quantities of quinidine. With intensive digitalis therapy to the point of toxicity, atrial fibrillation, normal sinus rhythm mixed with nodal rhythm, and finally a high nodal rhythm developed.

LEONARD S. GETTES, M.D., ARTHUR M. LEVY, M.D.,
JOHN S. HANSON, M.D., and BURTON S. TABAKIN, M.D., F.C.C.P.*
Burlington, Vermont

*Cardiopulmonary Laboratory, University of Vermont College of Medicine.

The Committee on Electrocardiography and Vectorcardiography welcomes comments. We would also be pleased to receive EKG's of exceptional interest with brief history. Please submit material to: Stephen R. Elek, M.D., chairman, 6423 Wilshire Boulevard, Los Angeles 48, California.

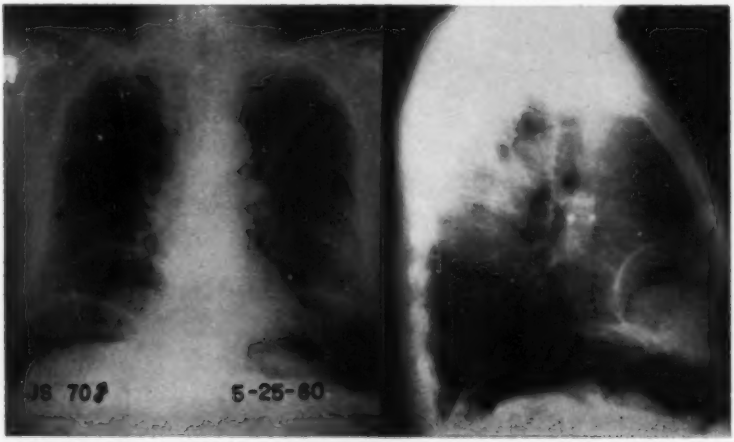
X-RAY FILM OF THE MONTH

Case History

A 70-year-old married white man who was admitted for study of a mass in the right hemithorax. In March, 1960 he was seen by his physician with a complaint of severe cough, productive of large amounts of gray sputum without hemoptysis. Chest findings on examination were minimal at that time. Symptoms persisted for two weeks. A photofluorogram taken at a mobile chest unit showed a large smoothly contoured semi-circular shadow in the right paracardiac area. He was referred to the City of Hope for diagnostic studies to determine the nature of this mass. Coronary insufficiency had been diagnosed 10 years previously but had not required treatment in recent years.

Posterior-anterior chest x-ray films obtained on admission on May 23, 1960 confirmed the presence of the mass, which at fluoroscopy was homogenous with smooth contours, located adjacent to the anterior chest wall and the right cardiophrenic angle. No visible pulsation was noted and during respiratory movements the mass moved opposite to the diaphragmatic movements. Planigrams did not show evidence of bronchi extending into the mass nor were any gas shadows present. On barium swallow a hiatus hernia could not be demonstrated. A film of the abdomen taken four and one half hours later showed barium outlining the colon up to the splenic flexure. The transverse colon had an inverted V appearance suggesting herniation of omentum through the foramen of Morgagni.

On May 25, 1960, 1000 ml. of air was instilled into the peritoneum without difficulty. X-ray films taken subsequently demonstrated the air to have passed into the space previously projecting as a mass in the right cardiophrenic angle. This confirmed the impression that the mass was made up of omentum herniating through the foramen of Morgagni. In view of the lack of symptoms, he was discharged without further studies.



Such herniations are relatively common and presumably due to congenital defects in the diaphragmatic musculature. Usually there is no sac; however in this case the x-ray films suggest that a sac may be present. The foramen of Morgagni is only one of several possible developmental defects through which herniation can occur, the most common, of course, being the esophageal hiatus. In addition, there may be herniation through traumatic defects in the diaphragm, or through defects created by failure of certain portions of the diaphragm to develop.

HASKELL J. WEINSTEIN, M.D.,* and FRED MARASSO, M.D.†
Duarte, California

*Director, Chest Hospital, City of Hope Medical Center, Duarte, California.
†Resident in Radiology, City of Hope Medical Center, Duarte, California.

The Committee on Chest Roentgenology welcomes comments. We would also be pleased to receive x-ray films of exceptional interest with a brief history. Please submit material to: Benjamin Felson, M.D., Department of Radiology, Cincinnati General Hospital, Cincinnati, Ohio.

Editorial

The Arden House Conference

Nearly a year has passed since the Arden House Conference was held to determine the best practical measures to pursue in the control of tuberculosis in the United States. The conference was co-sponsored by the United States Public Health Service and the National Tuberculosis Association, and was attended by some of the outstanding leaders in the nation in public health and tuberculosis control. Every physician is familiar with the spectacular gains made in the war against tuberculosis during the past decade, but not content with progress thus far, this group addressed itself to the task of formulating recommendations which, if carried out, should lead to the ultimate eradication of tuberculosis in the United States.

Practicing physicians have always had an important role in the control and treatment of tuberculosis. No substitute has yet been found to replace the private physician who is tuberculosis conscious and on the alert to diagnose it among his patients. With modern chemotherapy, the number of patients treated at home has increased, thus emphasizing more than ever the responsibility of the private physician regarding tuberculosis. Since the general practitioner often turns to the specialist in tuberculosis for guidance, it seems both timely and proper to report the high points of the findings and recommendations of the Arden House Conference to our readers, and to urge their cooperation as private physicians in applying these recommendations in their own practice.

The program as developed by the Conference is a bold one and requires the active cooperation of all national, state and local agencies, official and voluntary, which are interested in the control of tuberculosis. It also requires and deserves the full support of all private physicians.

Treatment Is the Tool

The chief recommendation of the Conference is a program for the application of adequate chemotherapy on a wide scale as a public health measure for the elimination of tuberculosis in the United States. Briefly stated, its goal is to adequately treat *all* cases of active tuberculosis when discovered, thus preventing further spread of the disease. A number of studies have demonstrated that nearly 90 per cent of previously untreated cases of tuberculosis can be rendered non-infectious by long-term combined chemotherapy; and, that the possibility of reactivation in these cases is minimized. Though this program emphasizes chemotherapy primarily as a public health tuberculosis control measure, the benefit to the individual patient is obvious. It also implies a continuing and effective case finding program that will uncover new active, or potentially active cases. If the case-detection part of the program is to be successful, private physicians cannot and must not shirk their role.

Because the problems involved in adequate control vary so widely in different states and localities, the programs will have to be tailor-made

to fit the needs of a given state or community. Methods of control which are adequate for rural Iowa or Minnesota, for example, will differ greatly from those employed in the economically depressed areas of New York City, Chicago or Los Angeles. The responsibility for developing these tailored-to-fit programs falls on the state and local public health authorities, aided wherever possible by voluntary agencies such as the tuberculosis associations.

Certain methods and procedures in case-findings, such as tuberculin testing and x-ray surveys are time-tested but need to be fitted to the requirements of a given locality or area. Funds, personnel and resources must be concentrated on those population groups with the greatest tuberculosis problem.

Intermediate goals, programs, priorities and performance standards should be reviewed at intervals and revised if changing conditions or situations warrant. These revisions may include both case-finding and treatment methods.

One of the most significant and exciting items on the agenda for discussion by the conferees was the one dealing with the use of isoniazid as prophylaxis. If early progress reports in this field are confirmed by longer term results, it will mean a major break through in TB control in this country. Controlled studies carried out under the auspices of the United States Public Health Service show that isoniazid is effective in preventing complications of primary tuberculosis in children. Based on the results of these studies, the Public Health Service makes the following minimum recommendations for the use of isoniazid to prevent extrapulmonary complications of primary tuberculosis:

> "All infants under one year of age who react to the tuberculin test, and all children from one to four years of age who have, in addition, x-ray evidence of primary tuberculosis should be given 5 mg. of isoniazid per kilogram of body weight every day for one year."

There is also considerable evidence accumulating that isoniazid will prevent active disease in tuberculin-positive adolescents and adults, particularly in recent converters. How long the prophylactic effect will last after the isoniazid has been discontinued remains to be seen. Further studies continued over a period of years will be necessary before these early promising results can be confirmed. In any event, the use of isoniazid as prophylaxis appears to be an effective tool in the control of tuberculosis and the Conference urgently recommends that these and similar studies be continued.

Reporting practices need to be reviewed and improved for these constitute an important gap in current TB control. Too many private physicians seem to avoid reporting their TB cases. Here the physician's responsibility is clearly defined. The fact that 25 per cent of deaths from tuberculosis had never been reported during the life of the patient points up another serious deficiency; and one which has remained essentially unchanged for the past 10 years.

The Conference recommended that adequate laboratory facilities be provided which are conveniently located to all physicians diagnosing and treating tuberculosis. The conferees were dismayed to learn that rela-

tively few hospitals or public health laboratories are using modern methods for the diagnosis and supervision of patients. Such laboratories should be able to ascertain by culture methods whether the organism is a true mycobacterium tuberculosis, or one of the many other strains of acid fast bacilli. They should also test the organisms for sensitivity to the commonly used anti-tuberculosis agents, so the physician may select the chemotherapy regimen most likely to be effective in each case.

The use of BCG vaccine was recommended by the Conference in appropriate situations and population groups where the risk of infection is high. The Conference, in effect, reaffirmed the policies of the Public Health Service and the American Thoracic Society (formerly the American Trudeau Society). The Conference also urged further research for a better, more effective vaccine.

The need for more research regarding the social, psychological and cultural factors involved in the tuberculosis problem was stressed by the Conference. As one conferee put it: "If we are going to improve services to the patient as a part of the drive to improve treatment as a whole, there must be investigation of the social factors."

The possibility of finding a new, and even simpler skin test than the Mantoux also came in for considerable discussion. The conferees expressed the hope that a test could be developed which would require no needle and yet be so simple, inexpensive and easy to apply that a physician or nurse need not be present. If such a hope can be realized, large numbers could be tested with a minimum of effort and expense.

The challenge posed by these Conference recommendations constitutes a tremendous stimulus to the campaign against tuberculosis. The conferees believe that if bold, decisive and continuous action is taken, the goal of eradicating tuberculosis from our midst can be reached. This goal and the program to attain it are worthy of the full support of all physicians.

KARL H. PFUETZE, M.D., F.C.C.P.
Chicago, Illinois

SIXTH INTERNATIONAL CONGRESS ON DISEASES OF THE CHEST

Vienna was host to the Sixth International Congress on Diseases of the Chest, August 27-September 1, 1960, presented under the patronage of the Federal President of Austria, Dr. Adolf Schärf, and sponsored by the American College of Chest Physicians, Council on International Affairs. Approximately 2,700 physicians and their families, representing 69 countries and territories throughout the world, registered for the congress. This is the highest registration ever attained at a College congress.

Professor Karl Fellinger of the University of Vienna served as President of the congress and Professor Anton Sattler, Regent of the College for Austria, was Secretary-General. Professors Fellinger and Sattler and the other members of the Organizing Committee are to be congratulated for the splendid scientific and social program arranged for the congress. The other members of the Organizing Committee were: Dr. K. H. Spitzy, Treasurer; Drs. F. Mlczoch, A. Balogh, G. Grabner, H. Jenny, A. Neumayr, P. Seiler and F. Schmidt. Mrs. A. M. Jörg served as Administrative Secretary. The College wishes to express its sincere gratitude to the above-named committee members as well as to the many other College officials and members in Austria, too numerous to list, for their efforts and generous cooperation in making the congress so successful.

We also wish to extend our appreciation to the following sponsors for their support and contribution to the Sixth International Congress:

Biochemie Ges. m.b.H., Kundl/Tirol, Austria
Ciba Ges. m.b.H., Vienna, Austria
Cilag-Chemie, Verkaufsgesellschaft chem.pharm. Produkte m.b.H., Vienna, Austria
Ennser Zuckerfabriks A.G., Enns, Austria
R. J. Geigy A.G., Basel, Switzerland
Hoffman-LaRoche, A.G., Basel, Switzerland
Hohenauer Zuckerfabrik der Bruder Strakosch, Vienna, Austria
Institut fur Medizinische Statistik, Ges.m.b.H., Frankfurt/Main, Germany
L. Novoting, Globe Slicing Machine Co., Inc., Stamford, Conn., USA
Pharmig, Vienna, Austria
Sandoz, A. G., Basel, Switzerland
Verband Osterreighischer Banken und Bankiers, Vienna, Austria
Vereinigung Osterreichischer Industrieller, Vienna, Austria

Inaugural Ceremony

The congress was officially opened with a magnificent Inaugural Ceremony held at the Imperial Palace (Hofburg) on Sunday evening, August 28. Professor Fellinger, President of the congress, presided, and representatives of the Austrian Government, the Government of the City of Vienna, the Faculty of Medicine of the University of Vienna, the Austrian Medical Association, and diplomats from many of the Embassies in Vienna were in attendance.

Officials of the American College of Chest Physicians on the stage at the Inaugural Ceremony of the Congress, Imperial Palace (Hofburg), Sunday, August 28, 1960.

The Vienna Symphony Orchestra opened the program with several musical selections. Professor Fellinger addressed the audience briefly and introduced Minister Heinrich Drimmel of the Austrian Government and Dr. Hans Mandl, Vice Mayor of Vienna, who welcomed the congress delegates to Vienna. The President of the American College of Chest Physicians, Dr. M. Jay Flipse, responded and then read the following message received from the Hon. Dwight D. Eisenhower, President of the United States of America:

> "It is a pleasure to send greetings to those attending the Sixth International Congress on Diseases of the Chest. This congress brings together scientists from many nations concerned with the health of their countrymen and their fellow men throughout the world. It is heartening to be reminded that such a meeting of trained and dedicated medical leaders is inspired by the highest and widest goals of service. I am delighted to add my best wishes for a successful congress."

Dr. M. Jay Flipse, President, and Dr. Hollis E. Johnson, President-Elect of the College, awarded diplomas to 120 new Fellows of the American College of Chest Physicians from many countries throughout the world. The distinction of Honorary Regent was conferred upon Professor Taizo Kumagai of Tokyo, Japan, and Dr. Miguel Canizares of Manila, Philippine Islands. Dr. Manuel Quisumbing, Manila, the Regent for the Philippines, received the certificate for Dr. Canizares who was unable to attend the congress.

Following a brief musical interlude, Professor Andrew L. Banyai, Chairman of the Council on International Affairs of the College, was introduced. The 1960 International Medal of the College was awarded by Professor Banyai to Professor Lopo de Carvalho, of Lisbon, Portugal, for his contributions to the specialty of diseases of the chest.

Professor Anton Sattler, Secretary-General of the congress, in his address, discussed the objectives of the congress and the program of activities. National flags were presented by officials from the following countries:

Ecuador—Dr. Jorge Higgins, Guayaquil

Egypt (U.A.R.)—Dr. Abdel Aziz Sami, Cairo

Finland—Dr. Risto J. Elo

France—Dr. Etienne Bernard, Paris

Greece—Dr. Basil Papanicolaou, Athens

India—Dr. Raman Viswanathan

Jordan—Dr. Wasif Kanaan, Amman

Lebanon—Dr. Papken Mugrditchian, Beirut

Norway—Dr. Per Wexels, Bergen

Philippines—Dr. Manuel Quisumbing, Sr., Manila

Spain—Dr. Antonio Caralps, Barcelona

These flags will be displayed at the College offices in Chicago, along with those presented at previous international congresses.

A certificate of Honorary Membership in the Ecuadorian Society for Diseases of the Chest was presented to Mr. Murray Kornfeld, Executive Director of the College, by Dr. Jorge A. Higgins, Governor for Ecuador.

Professor Fellinger gave the closing remarks and the Vienna Symphony Orchestra concluded the program with several selections.

International Committee Meetings

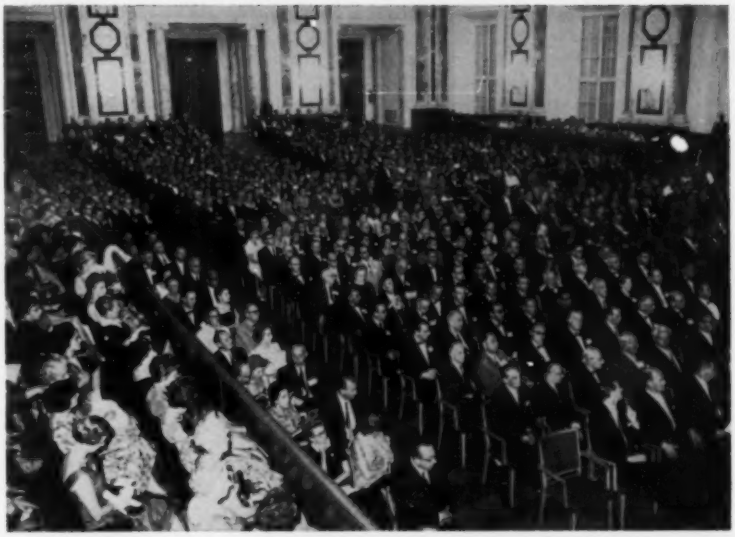
The meetings of the international committees were held on Saturday, August 27, at the University of Vienna, from 9:00 a.m. to 12:00 noon. Reports of the committee meetings have been submitted by the respective chairmen or secretaries and are being mailed to the members. The next meeting of the international committees will be held at the time of the Seventh International Congress on Diseases of the Chest and in the interim their activities will be conducted through correspondence.

Executive Sessions

The opening Executive Session was held at the University of Vienna on Sunday, August 28, at 2:00 p.m. and was attended by the Regents and Governors of the College, as well as other College officials, from more than 40 countries. Dr. M. Jay Flipse, President, presided and the following program was presented:

Message of Welcome
Karl Fellinger, Vienna, Austria, President of the Congress

Report of the Organizational Committee
Anton Sattler, Vienna, Austria, Secretary-General of the Congress



The Inaugural Ceremony of the Congress, Imperial Palace (Hofburg), Sunday, August 28, 1960.

Reports of the Councils on International Affairs
Andrew L. Banyai, Chicago, Illinois, Chairman

Council on Pan American Affairs
Jose Ignacio Baldo, Caracas, Venezuela, Chairman

Council on European Affairs
Attilio Omodei Zorini, Rome, Italy, Chairman

Council on Pan Pacific Affairs
Manuel Quisumbing, Sr., Manila, Philippines, for Miguel Canizares, Chairman

Council on Middle Eastern Affairs
Papken S. Mugrditchian, Beirut, Lebanon, Chairman

Council on Asian Affairs
Raman Viswanathan, Delhi, India, Chairman

Council on African Affairs
K. C. F. M. Seghers, Leopoldville, Congo, Secretary, for David P. Marais, Capetown, South Africa, Chairman

Reports of the International Committees

The closing Executive Session was held at the University of Vienna on Thursday afternoon, September 1, and Dr. Hollis E. Johnson, President-Elect of the College, presided. Reports were presented as follows:

Sixth International Congress
Karl Fellinger, Vienna, Austria, President
Anton Sattler, Vienna, Austria, Secretary-General

Committee on College Essay
Edward H. Morgan, Seattle, Washington

Committee on College Books
Alfred Goldman, St. Louis, Missouri

Board of Examiners
David B. Radner, Chicago, Illinois

Committee on Nominations
John F. Briggs, St. Paul, Minnesota

The following resolution was presented and unanimously adopted:

WHEREAS, The Sixth International Congress on Diseases of the Chest held in Vienna, Austria, August 27-September 1, 1960, has been most successful,

BE IT RESOLVED, That the officers and members of the American College of Chest Physicians extend their deep appreciation and sincere thanks to:

The President of Austria

The Mayor of Vienna

The President of the Congress, Professor Karl Fellinger

The Secretary-General of the Congress, Professor Anton Sattler

The Treasurer, Dr. K. H. Spitzy

The members of the Organizing Committee, Drs. Mlczoch, Balogh, Grabner, Jenny, Neumayr, Seiler and Schmidt.

The Ladies Committee, Mrs. Fellinger, Mrs. Sattler, Mrs. Kyrle and the other members of the committee

The Administrative Secretary, Mrs. A. M. Jorg

The Sponsors, Exhibitors, the Verkehrsburo and all of the cooperating hotels and all others who contributed to the success of the congress.

Dr. Jorge A. Higgins, Guayaquil, Governor of the College for Ecuador, announced the completion of a new building in Guayaquil which will be the headquarters of the American College of Chest Physicians in Ecuador. Through the efforts of Dr. Higgins, funds for the building were obtained. The officials of the College congratulated Dr. Higgins on his splendid achievement and expressed their hope to visit the new building.

Announcement was made by Mr. Murray Kornfeld, Executive Director of the College, that at a meeting of the Executive Council held in Vienna on Wednesday, August 31, invitations for the next international congress were considered. He reported that the Council had unanimously accepted the invitation submitted by the Government of India to hold the Seventh International Congress on Diseases of the Chest in New Delhi. Dr. Raman Viswanathan, Regent of the College for India, and chairman of the Indian Delegation, expressed the appreciation of the College members in India, as well as his Government, for acceptance of the invitation. The Indian Delegation pledged the complete support of the medical profession and the Government of India towards the successful organization of the next congress.

It was also announced that an invitation from Mexico to hold the Eighth International Congress in that country had been accepted. Dr. Donato G. Alarcon, Regent of the College for Mexico, and Dr. Miguel Jimenez, Governor, who extended the invitation in behalf of their government, extended a warm welcome to all delegates to visit Mexico in 1964.

The exact dates, as well as further information concerning the coming international congresses will be announced in the near future.

Congress Banquet

The Congress Banquet was held at the New Imperial Palace (Hofburg) on Wednesday night, August 31. During dinner a band provided Viennese music. The world-famous Vienna Boys Choir gave a recital of well-known songs, followed by a performance of the Vienna State Opera Ballet.

Professor Fellinger presided at a short program after dinner. The College officials and diplomats at the head table were introduced. Certificates of appreciation were presented to the College officials in Vienna for the organization of a successful international congress. Professor Fellinger presented certificates to the College officers in behalf of the Austrian members. Mr. Kornfeld announced that the Seventh International Congress would be held in New Delhi, India and the Eighth in Mexico. Drs. Raman Viswanathan, Regent for India, and Donato G. Alarcon, Regent for Mexico, were introduced and they extended a warm welcome to the College members to attend the congresses in their respective countries in 1962 and 1964. The closing remarks were made by Professor Anton Sattler.

Dancing in the beautiful adjoining ballroom climaxed the evening.

Scientific Sessions

All of the scientific sessions were held at the University of Vienna. Two main halls were used for the presentation of the formal lectures and panel discussions. Simultaneously, seven adjacent smaller halls held colloquia on various subjects. Another hall was used for the presentation of motion pictures on diseases of the chest each day. The program opened at 9:00 a.m. on Monday, August 29, and continued through each day until 5:00 p.m. on Thursday, September 1.

The scientific program was organized under the direction of Professor Andrew L. Banyai, Chairman of the Council on International Affairs of the College. He was ably assisted by Professor Ignacio Chavez of Mexico City and Dr. Felix Mlczoch of Vienna.

The Fireside Conferences were presented on Monday night, August 29, at the Vienna Stadthalle. Fifty subjects were discussed by groups seated at as many tables in the huge meeting hall. Refreshments were served to the thousand or more doctors attending the session. The conferences were televised for Austrian audiences, as well as filmed for motion pictures and newspaper coverage.

There were a large number of technical and scientific exhibits displayed at the University of Vienna for the congress. The leading Austrian and other European pharmaceutical and medical supply houses were represented in the technical exhibits.

One of the Fireside Conferences of the Congress, Vienna Stadthalle, ... day night, August 29, 1960.

Ladies Activities

The ladies committee, headed by Mrs. Karl Fellinger, Mrs. Anton Sattler and Mrs. Paul Kyrle, organized a lovely program of activities for the visiting ladies, including sightseeing tours of Vienna, the Vienna Woods, and the beautiful palaces and museums of Vienna. There was a special concert at the Palais Auersperg and a visit to the fashion school of Vienna. In addition, a "Heurigen" evening was planned for the ladies and their husbands at Grinzing. Officials of the College were invited to a reception at the Schonbrunn Palace given by the Austrian Government.

All of the social events for the delegates and their families were extremely interesting and beautifully planned. The closing night of the congress, Thursday, September 1, coincided with the opening of the Vienna State Opera and many of those attending the congress had the opportunity of hearing "Das Rheingold" and seeing the magnificent State Opera House. Performances were also being given at the Burgtheater of Vienna, which were attended by many delegates and their families.

Post Congress Tours

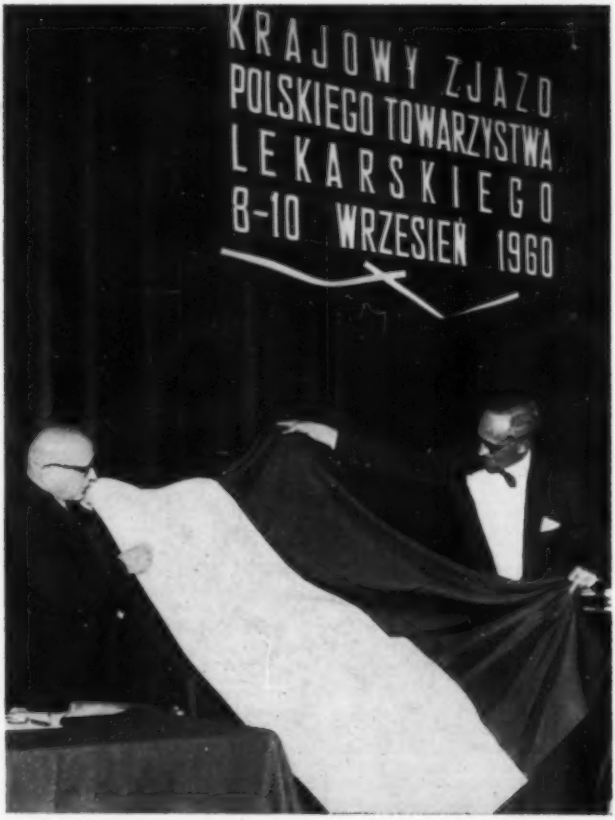
Three post-congress tours departing from Vienna on Friday, September 2, and ending in Paris on September 26, were planned for members of the College.

Tour A traveled from Vienna to Istanbul, Tel Aviv, Athens, Rome and Paris, by air. Forty members and their wives participated in this tour which provided the opportunity of meeting with the College members in the countries visited. The period September 2-7 was spent in Istanbul, Turkey and a scientific program of Fireside Conferences in which the Turkish members participated, was held on Monday, September 5. In Tel Aviv, Israel a scientific program was presented on Sunday, September 11, which was attended by 150 College members and guests. The Minister of Health was present at the meeting and welcomed the group to Israel. In Athens, Greece a scientific program was presented at the Popular Hospital on September 13, which was very well attended, and the Minister of Health gave a reception for the College group that evening. During the visit to Rome, Italy, many of the College members attended the European Congress of Cardiology, September 18-21, and a number of the physicians visited the Carlo Forlanini Institute. Many interesting sightseeing tours were made in the various countries visited and the members of the group were also entertained by the officials of the College in each country.

Twenty-four members participated in Tour B which took them to Russia, Poland, Italy and France. Their first stop was in Moscow, then Leningrad, both cities offering extremely interesting tours. During their visit to Warsaw, a scientific session was presented on September 10 in cooperation with the Polish Medical Association and the Polish Medical Alliance. The American Embassy gave a reception for the College group which was followed by a banquet at the Grand Hotel, sponsored by the Polish Medical Association in Warsaw. This was the first medical congress of American and Polish physicians in the 600-year old history of Polish medicine. The participants in Tour B then traveled through Italy, visiting Milan, Venice, Florence and Rome. In Venice they attended the International Congress on Bronchoesophagology, and in Rome, the European Congress on Cardiology.

Tour C, in which twenty-five members participated, toured by bus to Salzburg and Innsbruck, Austria, St. Moritz and Lugano, Switzerland, Venice, Florence and Rome, Italy. In Innsbruck some of the members attended the congress of the International Society for Preventive Medicine and Social Hygiene, September 4-6, and in Venice the International Congress on Bronchoesophagology, September 12-15.

A special charter flight for a group of College members was arranged with Pan American World Airways, which took them from New York to Vienna on August 24 and returned from Paris on September 26. The Cartan Travel Bureau, Chicago, official travel agent for the College, was in complete charge of the tours and is to be congratulated on the splendid arrangements.



Professor Marian Kacprzak (left) presenting the Polish flag to the American College of Chest Physicians. Dr. Benson Bloom, Albuquerque, New Mexico (right) receiving the flag. The presentation was made at a meeting sponsored by the Polish Medical Association and the Polish Medical Alliance in Warsaw on September 10.

BOOK REVIEW

VASCULAR SPIDERS AND RELATED LESIONS OF THE SKIN. By William B. Bean, M.D. Charles C. Thomas, Springfield, 1958; 372 pages, 130 illustrations, $8.50.

For an author to write a book review of his brain-child is as risky and heady an experience as criticizing one's own wife or child. Also it may produce some of the same sensation as writing your own obituary. Any book written by someone deeply immersed in a subject contains much autobiography. Reviewing one's own book then becomes a form of auto-biography. I shall begin my comments with a series of quotations. "I was discouraged and a little disillusioned that none of my splendid clinical teachers at John Hopkins, Harvard, or Cincinnati could answer my annoying questions about spiders. I began to collect data, studying spiders wherever I found them, approaching them from all sides and in all places." "Anyone's review of his own motives is apt to be distorted by conscious or unconscious shifts of emphasis as well as by the subtle reinterpretation which time brings." "If clinical trivia and ephemera illustrated no general principles in medicine I would not care. I have never been able to stimulate or simulate interest in popular medical problems just because they were popular. Nevertheless small lesions may help us understand larger ones and lead to generalizations bearing directly upon practical medicine." "No part of development, growth, normal function, disease, aging or death is without its ultimate vascular context. In spite of these truisms and in spite of much desultory and concerted study there are large sums of ignorance which disfigure and Balkanize in separate, mutually excluding systems our knowledge of blood vessels."

The organization and plan of the book need some comment. By far the longest chapter deals with spiders and palmar erythema. Thereafter, the vascular lesions of the skin are grouped about a common etiologic mechanism or process, a region of the body, or a common clinical complication. Since several might have been put in more than one place, the Table of Contents indicates this in the headings of several chapters. For instance, hereditary hemorrhagic telangiectasia, which I call Osler's disease, appears in the chapter on congenital lesions but might have appeared with vascular lesions which increase with aging, or the chapter on enteric bleeding with diagnostic skin lesions.

"With the exception of Fabry's syndrome and epidemic dropsy, I have observed all the lesions and disorders under discussion. My own personal contributions to natural history include the first relating of spiders and palmar erythema to both liver disease and pregnancy, the use of infrared photography to produce vascular obliteration of red lesions as well as to accentuate the appearance of blue ones, an elaboration of the dermovascular changes in the syndrome of metastatic carcinoid, the demonstration of secular changes in the lesions of Osler's disease and the dynamic state of changing patterns of small vessels in normal skin, too. I have brought together the congenital dysplastic angiectases showing a tangential relation to Maffuci's syndrome while trying to escape the anachronistic errors of eponyms by avoiding many but using some . . . I am not aware that others have described venous lakes, palmar varices, striate atrophy of the skin, dysautonomia in the adult or the combination of vascular lipomas, ophthalmoplegia, steatorrhea and phlebectasia into a possible syndrome, but I have not searched all possible repositories, or even many textbooks or dermatology. The history of medicine reveals that very few people really discover anything new and many whose names are tacked onto a lesion or syndrome may be embarrassed to learn that others not only have described it before, but better. I could not care less. At least I have resuscitated if not discovered many interesting vascular lesions."

Illustrations are a major problem in any book dealing with visible lesions of the skin. There are two colored plates with a total of eight individual photographs. The picture of palmar erythema is especially good, and except for the blurring of detail in the spider covered with oil, the colored photographs convey their message. There are a total of 130 illustrations, not all of which give a very clear indication of the exact appearance of the lesion or process under discussion. Most of the photographs of spiders ar good, the histopathologic sections excellent, and the line drawings effective. Some of the photographs of palmar erythema are not very clear. A number of the comparisons of black and white and infrared photography present most excellently the startling contrast in such photographs. Several of the pictures of Osler's disease turned out excellently; a few poorly. One of the most striking series of pictures is the general physical appearance and x-rays of a patient with Maffuci's disease, taken over a 15-year span. Emphasis on the occurrence of a specific "blue rubber-bleb nevus of the skin and gastrointestinal tract" identifies a rare but easily recognizable syndrome. The photographs of mottling of the skin are for the most part not clear enough to add much. The mysterious anemic halo is emphasized and venous lakes, which hitherto have been totally overlooked, are emphasized.

In addition to the discussion of vascular spiders and palmar erythema, there are chapters on vascular lesions caused by humoral mechanisms, congenital and hereditary lesions and birthmarks, functional flushes and vascular patterns, neoplastic lesions, traumatic vascular lesions, vascular lesions which increase with aging, abdominal and thoracic venous structures, a digussion on nails and liver disease, enteric bleeding in patients with diagnostic skin lesions, and a miscellaneous section on lesions which defied classification. The references, nearly 1,000, are listed alphabetically and by

number. The text is not broken up with a great many numerical superscripts or subscripts, the author's name indicating which reference is indicated except when there might be some confusion. Giving the full title, as well as the author and journal or publisher of each reference, facilitates the use of the references for bibliographic purposes. There is a further breakdown listing all the references which have any bearing on the major subjects for extensive review if anyone is so inclined. There is an ample index and this with the full Table of Contents makes it easy to use the book for reference or cross-reference. My conscientious efforts to make this a nearly perfect book naturally fell short of realization. I did not read the whole book again in review but have found one or two garbled sentences, at least one consistent misspelling of a French word, one example of the wrong font of type and the mislabeling of two of the plates near the end of the book. A good many of the chapters begin with verses or quotations ranging from my parody on Little Miss Muffet from Mother Goose to Oliver Wendell Holmes. One or two outrageous limericks may stir the ire of spinsters of either sex, those shriveled medical creatures, devoid of humor, who prefer a somber and melancholy atmosphere about everything medical.

Whether I have made a substantial contribution to clinical medicine or not remains for the future to judge, but this is a book which should be helpful in clinical diagnosis and has something of importance for physicians in every specialty in medicine. Surgeons as well as internists will profit by its study; and, trespassing as it does on some of the uncultivated and fallow meadows of dermatology, it should be of interest to specialists in skin disease whose thoughts are more than skin deep. Specialists in thoracic disease may find interest in the zona corona, cervical fringes, and capillary markings as well as clubbing of the nails. Even a urologist might find Fabry's syndrome, pheochromocytoma, pulsating metastasis from hypernephroma and a few other items of help. This large miscellany of vascular lesions of the skin in one book assembles rare and common, important and unimportant disorders, lesions or marks for study in convenient form. The price seems high but color plates are costly and the publisher has a long way to go before he can share a modest tithe with the author.

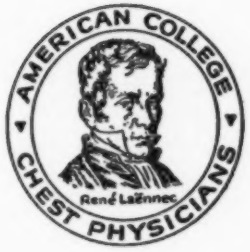
WILLIAM B. BEAN, M.D., F.C.C.P.

When a physician prepares a manuscript, he usually has more information on its subject than anyone else. Moreover, by the time the book is published, the author is thoroughly acquainted with its shortcomings as well as its values. When this classic, VASCULAR SPIDERS AND RELATED LESIONS OF THE SKIN was received for review, it was so unique, contained so much information known to very few persons and brought together in book form for the first time, that it seemed certain it would become a collector's item. Therefore, the author, himself, was asked to write a review for publication. After much urging, Doctor Bean prepared this review with great reluctance but to the complete satisfaction of the journal. *J. A. M.*

DISEASES

of the

CHEST



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DISEASES OF THE CHEST
AUTHOR INDEX

VOLUME XXXVIII—JULY-DECEMBER, 1960

DISEASES OF THE CHEST
SUBJECT INDEX

VOLUME XXXVIII—JULY-DECEMBER, 1960

CONTENTS

Number 1, July, 1960

Number 2, August, 1960

Number 3, September, 1960

Number 4, October, 1960

Number 5, November, 1960

Number 6, December, 1960

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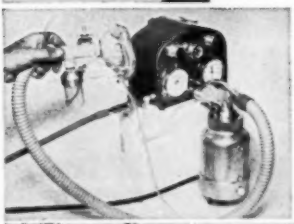

Is more comfortable for the patient, more penetrating and carries solution reagents to the site of mucous plugging and infection.

Warm air carries more moisture.

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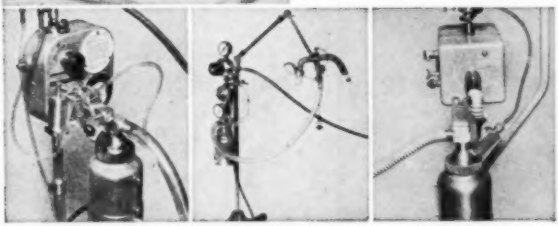

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- **Disposable needle cartridges ELIMINATE CROSS-INFECTION.**
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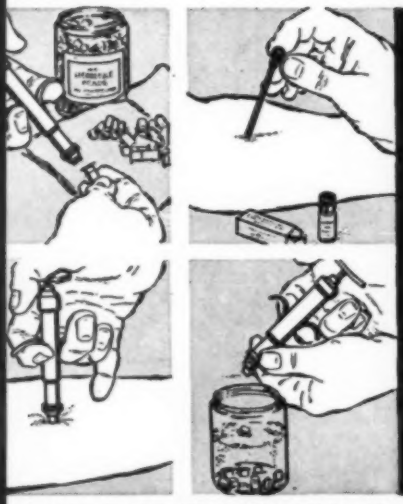

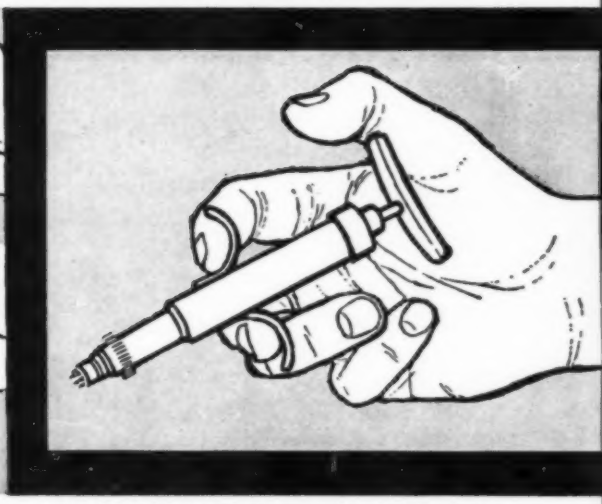

Procedure for STERNEEDLE TUBERCULIN TEST:

Top, left...Slip needle cartridge on gun with plastic applicator. Remove applicator.

Top, right...Place a drop of tuberculin PPD on cleansed forearm.

Bottom, left...Place gun on drop of tuberculin PPD. Pressure and release of handle automatically triggers and retracts the needles.

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